EXHIBIT T

September 15, 2015

Expert Report of Shelby F. Thames, Ph.D.

Prepared for

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL No. 2327**
THIS DOCUMENT RELATES TO THE CASES LISTED BELOW	**JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

Mullins, et al. v. Ethicon, Inc., et al.	*2:12-cv-02952*
Sprout, et al. v. Ethicon, Inc., et al.	*2:12-cv-07924*
Iquinto v. Ethicon, Inc., et al.	*2:12-cv-09765*
Daniel, et al. v. Ethicon, Inc., et al.	*2:13-cv-02565*
Dillon, et al. v. Ethicon, Inc., et al.	*2:13-cv-02919*
Webb, et al. v. Ethicon, Inc., et al.	*2:13-cv-04517*
Martinez v. Ethicon, Inc., et al.	*2:13-cv-04730*
McIntyre, et al. v. Ethicon, Inc., et al.	*2:13-cv-07283*
Oxley v. Ethicon, Inc., et al.	*2:13-cv-10150*
Atkins, et al. v. Ethicon, Inc., et al.	*2:13-cv-11022*
Garcia v. Ethicon, Inc., et al.	*2:13-cv-14355*
Lowe v. Ethicon, Inc., et al.	*2:13-cv-14718*
Dameron, et al. v. Ethicon, Inc., et al.	*2:13-cv-14799*
Vanbuskirk, et al. v. Ethicon, Inc., et al.	*2:13-cv-16183*
Mullens, et al. v. Ethicon, Inc., et al.	*2:13-cv-16564*
Shears, et al. v. Ethicon, Inc., et al.	*2:13-cv-17012*
Javins, et al. v. Ethicon, Inc., et al.	*2:13-cv-18479*
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Lambert v. Ethicon, Inc., et al.	*2:13-cv-24393*
Cook v. Ethicon, Inc., et al.	*2:13-cv-29260*
Stevens v. Ethicon, Inc., et al.	*2:13-cv-29918*
Harmon v. Ethicon, Inc., et al.	*2:13-cv-31818*
Snodgrass v. Ethicon, Inc., et al.	*2:13-cv-31881*

Miller v. Ethicon, Inc., et al.	*2:13-cv-32627*
Matney, et al. v. Ethicon, Inc., et al.	*2:14-cv-09195*
Jones, et al. v. Ethicon, Inc., et al.	*2:14-cv-09517*
Humbert v. Ethicon, Inc., et al.	*2:14-cv-10640*
Gillum, et al. v. Ethicon, Inc., et al.	*2:14-cv-12756*
Whisner, et al. v. Ethicon, Inc., et al.	*2:14-cv-13023*
Tomblin v. Ethicon, Inc., et al.	*2:14-cv-14664*

I have been asked to analyze Ethicon's Gynecare TVT medical device used for the treatment of stress urinary incontinence and offer opinions concerning claims that the TVT mesh used in Ethicon's product is not suitable for implantation. I have analyzed several other claims involving Ethicon's TVT devices used for the treatment of stress urinary incontinence. Accordingly, I have included in this report my analyses of these products. I have also included in this report critiques of other expert reports offered in this and other cases in which Ethicon's TVT products have been at issue.

Ethicon's TVT product is made of Prolene mesh. Prolene is the Ethicon brand name for its mesh material. Chemically, Prolene consists of polypropylene plus the addition of five highly proprietary additives as discussed herein. Where I refer to polypropylene used in Ethicon's mesh, I am referring to the specific polypropylene and proprietary additives that make this mesh different from mesh marketed by other manufacturers. All my opinions herein are offered to a reasonable degree of scientific certainty.

I have been asked to do the following:

- Address the issues of Ethicon's TVT as a material for use in the human body, its suitability for *in vivo* use considering its chemical and physical properties, propensity for degradation, material strength and viability, as well as longevity.

A copy of my Curriculum Vitae is attached as Appendix A. The materials I reviewed and/or relied upon in connection with the preparation of this report are listed in Appendix B. I am being compensated for my work in this matter at a rate of $400.00/hour.

In addition, I have directed the work performed by Kevin L. Ong, Ph.D., P.E. regarding cleaning, inspecting, testing and analyzing mesh explants, and I further rely upon the facts, opinions and data reflected in his expert reports. I also rely on my prior testing, reports, and appendices prepared in this litigation.

Ethicon's TVT device made from Prolene is suitable for its intended use. Polypropylene (PP) has been used in medical devices for decades, and for good reason.[1,2,3] It is a polymeric species of the propylene monomer and is a durable, thermoplastic polymer composed of carbon and hydrogen. Polypropylene offers mechanical properties of durability and elasticity and is the lightest major plastic with a density of 0.905 g/ml and the crystallizability of isotactic polypropylene makes it the polymer of choice for properties of commercial interest.[4,5]

The monomer propylene (CH_2=CH-CH_3) shown in Figure 1 when polymerized, gives polypropylene; a polymeric species (many monomers) where many monomers are attached through carbon to carbon bonds, Figure 2.[6] The process of combining monomers together to form larger molecules is termed polymerization. Stated differently, a polypropylene polymer is a chain of propylene monomers linked together. Changes in process conditions and catalyst can lead to production of three configurations of polypropylene, and in the current instance isotactic polypropylene (iPP). The isotactic form of polypropylene possesses the configuration wherein the side-chain, or pendant –CH_3 (methyl) groups are aligned on the same loci of each tetrahedral carbon atom thereby forming an "iso" configuration (polypropylene) arrangement of each main-chain carbon atom shown in Figure 2.[7]

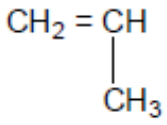


Figure 1. Propylene

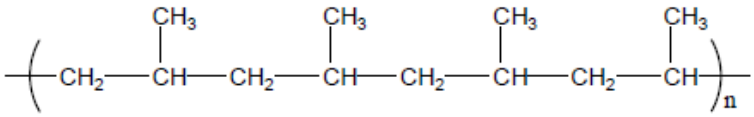


Figure 2. Isotactic form of polypropylene (iPP)

It is significant that PP consists only of carbon and hydrogen atoms. This organic composition of only carbon and hydrogen and its structure favors inertness, or in layman's terms, a material that is non-reactive to most environments. PP contains no polar groups such as sulfur, nitrogen, or oxygen. Such groups are different in electronegativity than carbon and thereby when present, create a molecular environment of polarity to PP.[8] However, with all main-chain carbon atoms of the same electronegativity, the PP molecule is homogeneous in electron density and thus is not polar. Therefore, there is no driving force for polar (species with negative or positive character) chemicals to be attracted to PP. An example of this concept is PP's high resistance to a common polar molecule, e.g. water (H_2O). Although it is very difficult to create a polymer, or anything else for that matter, unreactive in all environments, the choice of a hydrocarbon polymer like PP is as good as one can get for this application, and was the proper choice for Ethicon. The only supposedly truly inert material is gold, and even it is reactive to aqua-regia, a mixture of concentrated nitric and hydrochloric acids. I am unaware of any completely inert material.

The term "degradation" is commonly used to describe structural modifications from its pristine state.[9] However, I prefer "aging process" as molecular changes occur with time and use; such changes may be favorable or unfavorable. The process of molecular change is a function of use environment, chemical structure, and polymer composition. With respect to isotactic polypropylene (iPP), it is a chain of identical monomers linked

or bonded together, and, like other materials, it resists change but when change occurs, it is generally a function of environment and temperature. A structural change process seeks molecular site(s) most susceptible to change or alteration. For instance, if a hetero-molecular species such as an organic ester is used in an aqueous or water medium, a major concern would be hydrolysis wherein formation of an acid and alcohol would result. This change could be favorable should one desire to form an acid or alcohol, but unfavorable if ester stability was the intent. In the latter, it would be better to select a non-aqueous use environment or a different polymer type.

In general, the following are contributing factors to molecular changes:

(1) Light interactions

(2) Temperature-especially elevated temperatures

(3) pH

(4) Water

(5) Environment which may be in one or a combination of 1-4.

From a molecular formula perspective, PP favors inertness because there is nothing in its polymer chain to: (1) attract water; or (2) that an acid or base would want to attack. It possesses no inherent polar groups, and not surprisingly, is water insoluble.[10] Furthermore, temperature exposure is minimal given body temperature (i.e. 37ºC). The pH or acid-base characteristics of the body are very modest.[11] Its use is in the body and therefore is not exposed to sunlight or external elements. PP is sensitive to sunlight, and can undergo significant changes in the exterior if not protected by ultraviolet inhibitors.[12]

It is not surprising, therefore, that the chemical composition of a polymer can introduce sensitivity to one or more of these factors. Although the degree of exposure to any of these is important, exposure to light and water in combination with temperature are, in my view, potentially the most likely to initiate and affect subsequent molecular changes.

UV LIGHT

In the present instance, the effect of light is not a factor because the mesh is not exposed to ultraviolet (UV) light *in vivo* and possesses more than sufficient physical properties such as strength, elasticity and toughness. The structure of Prolene and/or PP can be altered by exposure to ultraviolet radiation.[7]

TEMPERATURE

Likewise, temperature is not a factor of degradation for iPP *in vivo*. It is well known that high temperatures favor thermal degradation but, the thermal stability of iPP is well beyond that of the use environment (37ºC). Several properties of Ethicon's Prolene were confirmed by testing a pristine Ethicon TVT device No. 810041B. Differential

Scanning Calorimetry (DSC) confirmed Prolene's melting point of 162.6ºC or 325ºF (Figure 3). Its excellent thermal stability was established by thermo-gravimetric analysis (TGA), with weight loss beginning only at 333ºC or 631ºF (Figure 4). Consequently, *in vivo* thermal stability is clearly not an issue or concern, and physical property determinations confirm the suitability and toughness of the Prolene fiber.

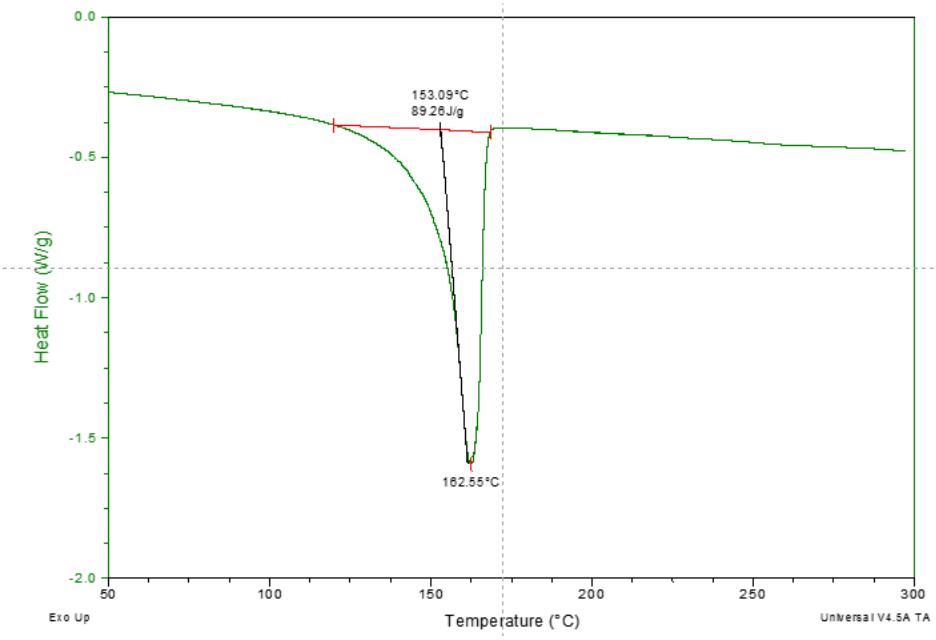


Figure 3. Differential Scanning Calorimetry (DSC) of pristine Ethicon TVT device No. 810041B – Lot 3694576

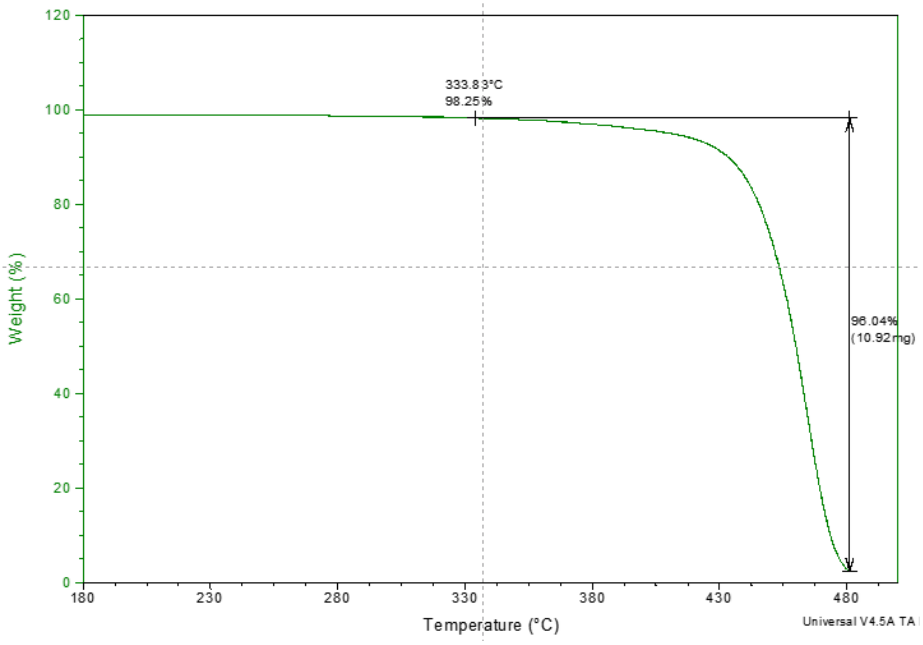


Figure 4. Thermogravimetric Analysis (TGA) of pristine Ethicon TVT device No. 810041B – Lot 3694576

pH:

The degree of acid or basic character is defined by pH. The scale of pH is from 1 to 14, with values below 7 being considered acidic, and values above 7 basic. Seven is considered neutral on the pH scale. Highly acidic materials (less than pH 7) are materials such as sulfuric acid, nitric acid, hydrochloric acid, and to a lesser extent, acetic acid while basic materials (higher than pH 7) for example are lye and ammonia. The human body is neither highly acidic nor highly basic.[13] pH is a function of the hydrogen ion concentration (H^+) and since PP possesses no polar character such as H^+ it has no pH.

WATER RESISTANCE:

Prolene and PP are very water resistant, highly water insoluble, and polyolefins like PP are also highly impermeable to water vapor.[14] PP's resistance to water and water vapor, along with its other properties herein enumerated, make it an ideal polymer for *in vivo* applications. By way of example and noted earlier, it is well known that polyesters, as hetero chain polymers, are sensitive to hydrolysis whereby the carbonyl-ester linkage is split into an alcohol and the respective acid.[15] Should the ester functionality be a portion of the polymer backbone, polymer degradation by hydrolysis occurs; not so with PP given its continuous carbon-carbon, non-polar, and water resistant backbone skeleton. Williams further notes that "the activation energy for the degradation of high molecular weight polymers used in surgery vary from 30 kcal/mole to 80 or 90 kcal/mole, and such reactions generally require either heat, UV light or high energy radiation, preferably in the presence of oxygen, to proceed. It seems certain from these conditions that no such degradation should occur within the confines of the human body."[16]

In conclusion, I do not believe that Ethicon's Prolene undergoes meaningful or harmful degradation *in vivo*. I am bolstered in my belief by a forward-looking seven year dog study conducted by Ethicon in November, 1985 and reported October 15, 1992, and my personal investigations.

The Burkley dog study was undertaken to determine long-term stability of implanted Prolene sutures.[17] D. Burkley of Ethicon utilized FTIR spectroscopy to identify suture material, as more than one polymeric product was involved in the study. He reported IR spectra of Prolene and conservatively noted "possible evidence of slight oxidation" via "a broadened weak absorbance at about 1650 cm^{-1}." However, I believe this to be a mis-assignment because it is unclear how the explants were cleaned and processed, if at all. This absorption frequency is within the range of proteins which would be expected to be present on the Prolene surface after years of implantation. He further performed gel permeation chromatography (GPC) to determine molecular weight

(polymer size) of explanted and pristine Prolene suture controls. The seven year data confirmed no significant difference in molecular weights for the 4/0 Prolene control suture and the seven year explants. These are significant data and confirm Prolene *in vivo* stability over the 7 year period. The Prolene study continued with examinations via light microscopy, scanning electron microscopy, and physical property testing.

Burkley performed physical property determinations via measurements of tensile strength, elongation, and modulus. These are extremely valuable data and very instructive in understanding the exceptional durability of Prolene during and after *in vivo* implantation. The elongation of explanted sutures increased 111% over the seven-year period, tensile strength diminished by only 5%, and modulus decreased by 70%. The net result is a durable, strong, elastic, tough, and pliable suture after 7 years implantation.

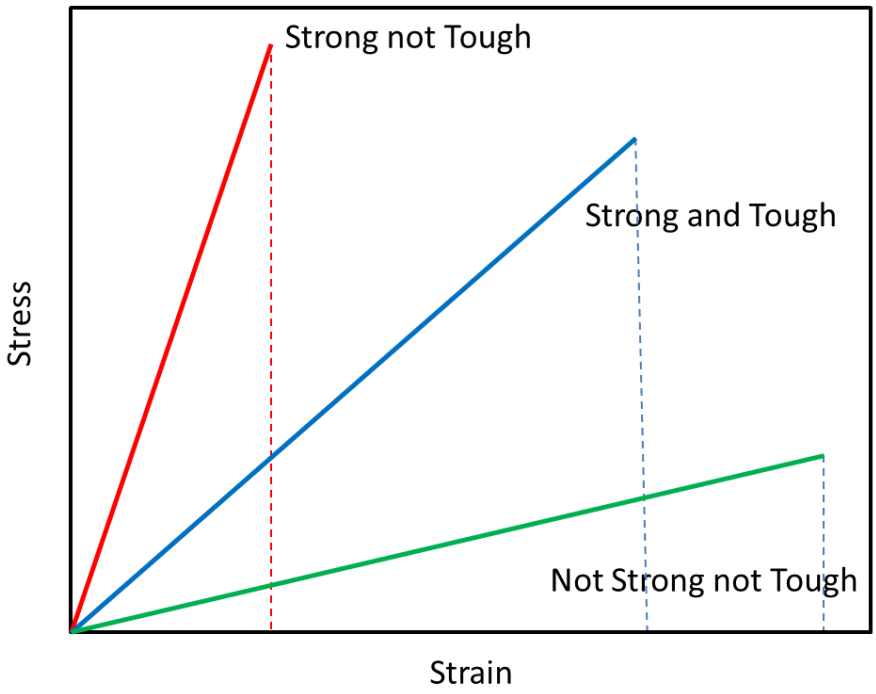


Figure 5. Stress-Strain Curve of Polymers Types

Figure 5 demonstrates the relationship between tensile strength (stress) and elongation (strain) for polymeric materials such as the TVT product that Ramirez received. The ultimate tensile strength is defined as the tensile strength at which a polymeric material (in this case Prolene) breaks and the ultimate elongation is the elongation at rupture.[18] In viewing Figure 5, it is evident that less elastic materials possess high strength and break at a relatively low percent elongation. These materials are strong, but not very elastic, and therefore not tough. Very elastic materials are those with high elongation requiring little stress to elongate the sample; these materials are not strong and not tough. However, materials requiring both high stress and elasticity before breaking are considered tough and durable (e.g. polypropylene). Toughness is defined as the area under the stress-strain curve.[19,20]

For instance, when the tensile strength and elongation data from Burkley's 7 year dog study are extrapolated and plotted (Figure 6) it is clear that implantation over the 7 year period did not adversely affect mesh toughness; instead, its physical properties improved. This is not unexpected because plasticization can improve polymer toughness.[21] It is well known that plasticizers are used to reduce intermolecular interactions and facilitate molecular mobility and, in doing so, can reduce tensile strength with a corresponding increase in elongation.[22,23,24] The plasticization/toughening effect is precisely what is manifested in the Burkley report and demonstrated in Figure 6.

Clearly, if toughness is improved after the initial implantation, as noted by the area under the stress-strain plot (Figure 6), there is absolutely no suggestion of, or support for, Environmental Stress Cracking (ESC) as a destructive mechanism during implantation or any other evidence of degradation. Moreover, it is reported that PP is "completely free from environmental stress cracking."[25] Others attempting to establish conditions for ESC of PP have not been successful.[26]

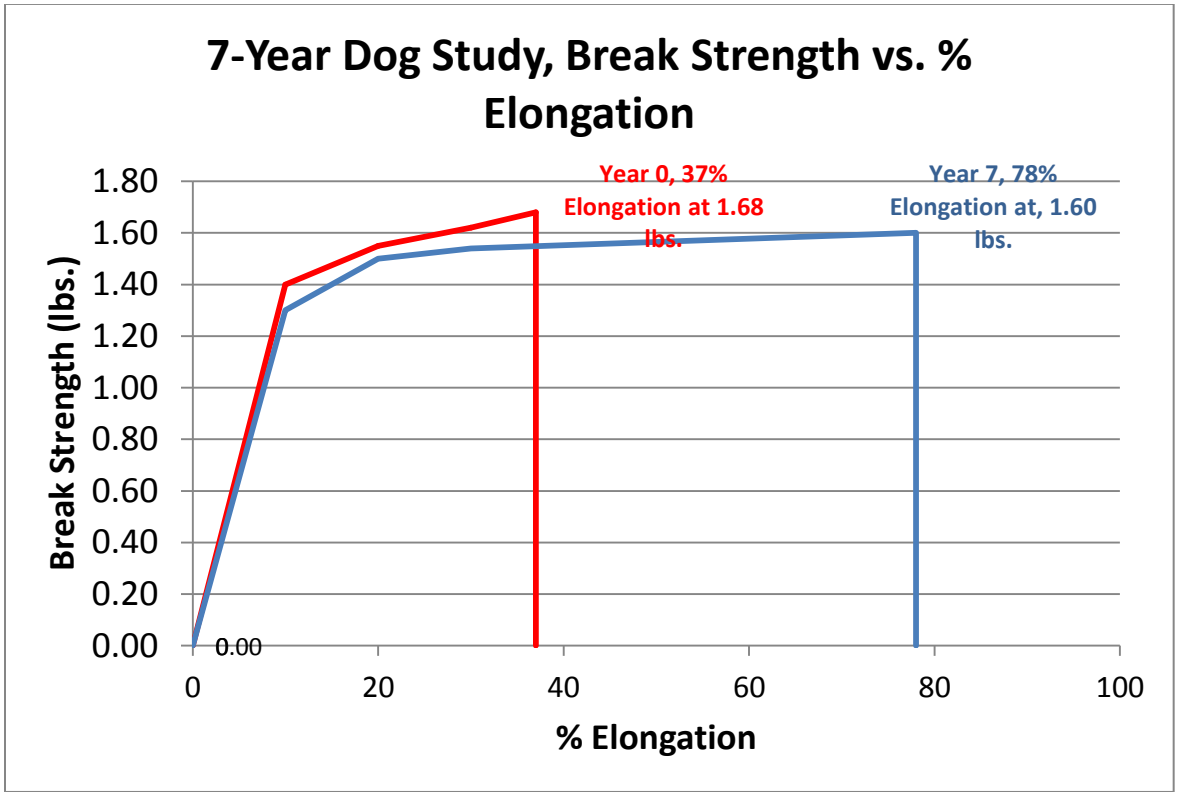


Figure 6. Plot of Burkley 7 Year Dog Study Data

In further support of *in vivo* stability of Prolene, Burkley performed molecular weight determinations by Gel Permeation Chromatography (GPC) and found no meaningful change over the 7 years of implantation. These data are exceedingly important, instructive, and are consistent with the physical property (toughness) data already noted. For instance, it is well known that molecular weight reductions adversely affect

physical properties.[27] Gahleitner and Fiebig discuss physical and chemical changes in materials as a function of molecular weight in the following statement, "In contrast to other polyolefins, such as PE or most olefin-elastomers (EPR, ethylene-propylene-diene rubber (EPDM), radical reactions in PP cause mainly a degradation effect, reducing the average chain length of the polymer and especially affecting the high molecular weight fraction. As these are of primary importance for the mechanics of the system-through their activity as inherent nucleants as well as their function as 'tie molecules' between different crystalline sections-a significant reduction of mechanical properties can also be expected. The normal consequence is embrittlement, a massive decrease in toughness."[28]

Taken in totality, Burkley's physical property/toughness data validates toughness improvement after the initial implantation. Burkley molecular weight data proved no meaningful loss of molecular weight. Had there been a change in molecular weight after implantation, Burkley would have found a massive decrease in toughness of the explanted sutures, as well as suture embrittlement as taught by Gahleitner and Fiebig.[29]

Burkley's study is further supported by the work of plaintiffs' expert, who performed molecular weight determinations of Carolyn Lewis and Linda Batiste explants, two TVT cases made of Prolene, and Mrs. Bellew's Prolift explant, which is also made of Prolene. The plaintiff's expert report was consistent with that of Burkley as neither found molecular weight losses for either explant.

These data are consistent with no molecular weight changes after 7 years implantation, and are supported by published work of George Wypych who stated "Molecular weight of PP decreases on exposure to UV radiation due to the chain scissions in surface layers."[30] Had Burkley or plaintiff's expert found molecular weight changes, tensile strength, elongation, and toughness properties would have declined precipitously.

These authors also report "Tensile strength and strain values change linearly with carbonyl index concentration," or simply the accumulation of carbonyl groups with exposure or use time.[31] Carbonyl groups are well known to be a primary product of PP degradation. It is given that if carbonyl groups develop during use, molecular weight losses of PP will occur. It is therefore obvious that molecular weight and carbonyl group formation or appearance are inextricably linked and you cannot have one without the other as noted in Figure 7.

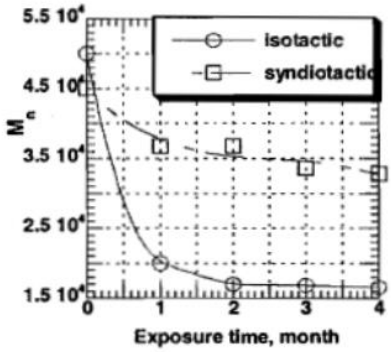


Figure 14.107. Number average molecular weight of iso- and syndiotactic polypropylenes vs. irradiation time with mercury lamp through Pyrex filter. [Data from Kato, M; Tsuruta, A; Kuroda, S; Osawa, Z, *Polym. Deg. Stab.*, 67, No.1, 2000, 1-5.]

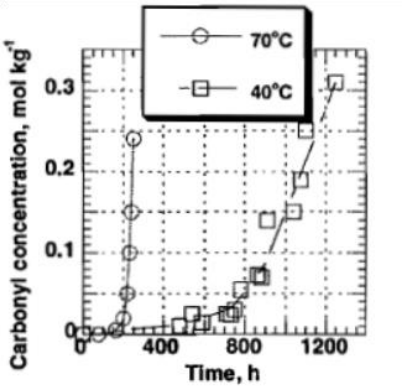


Figure 14.108. Effect of temperature on carbonyl group concentration in polypropylene exposed to fluorescent lamp radiation in the range of 300-500 nm. [Data from Audouin, L; Girois, S; Achimsky, L; Verdu, J, *Polym. Deg. Stab.*, **60**, 1, 137-43, 1998.]

Figure 7. Relationship between molecular weight and carbonyl group formation in polypropylene.[32]

Burkley's 7 year dog study findings are consistent with the following data in that

- Prolene's molecular weight did not change over the 7 years of implantation,
- nor were there carbonyl absorption frequencies sufficient to determine a carbonyl index concentration, and
- physical properties of the Prolene explant did not deteriorate, but instead, improved during implantation.
- Prolene is stable during implantation

Had degradation occurred, there would have been significant losses in toughness, molecular weight, and a concomitant increase in carbonyl frequency; none of which occurred during the 7 year dog study.

In summary, plaintiff experts' arguments for degradation, oxidation, and molecular weight losses after initial implantation are not supported by Burkley's data, plaintiff's data, or published literature developed from reliable scientific data.

I understand there are those who allege Prolene's structural changes in vivo are sufficient to affect property/device function loss. However, this tenet is not founded on factual, reliable and repeatable scientific data of which I am aware. It is my opinion, and supported by extensive and repeatable experimental data, that such proponents have historically, and erroneously, identified adsorbed protein coatings on the implant surface as polypropylene; they are mistaken. The adsorbed protein coating forms *in vivo*, and is subsequently "fixed" by the chemical reaction of formaldehyde with proteins. The fixation product, with one exception, has not been removed, in the instances of which I am familiar, prior to explant testing and evaluation. Thus, these proponents have

mischaracterized adsorbed protein coatings as PP, and, to date, the scientific and chemical basis of their argument is non-existent. The work of de Tayrac and Letouzey, the one exception that did not use formaldehyde as a fixation agent, further confirms this precept. De Tayrac writes that "The explanted infected mesh shows transverse cracks (a). After washing with DMSO (b) and ultrasonic shock (c), it appears marked modifications in mesh surface corresponding to the biofilm (a), and after biofilm removal, no polymer degradation was seen any more(c)." (a, b, and c are photos of explanted PP at the various stages of cleaning). Note, contrary to others who report PP degradation, de Tayrac did not "fix" the proteins of his sample via immersion in formalin (formaldehyde in water) solution. This is extremely significant as the fixation process produces a hard, insoluble, and brittle protein-formaldehyde polymer composite shell surrounding the PP fiber. It is significant that de Tayrac's decision not to use formalin fixation as part of his experimental protocol allowed him to examine the PP fiber without interference of the encapsulating protein-formaldehyde polymeric composite. Consequently, he was able to clean the fibers with mild reagents and conditions. In summary, when properly handled and cleaned without "fiber fixation", the PP fibers were devoid of a protein coating layer and essentially unchanged.

Much has been written, and literally thousands of experiments conducted, in an effort to ascertain the interrelation of synthetic mesh materials, their function, and performance in the human body. In studying these issues, I have confirmed an alarming and almost universal indifference for the underlying basic chemistry/biochemistry necessary for evaluating the efficacy of mesh materials. For instance, the typical protocol for dealing with a patient complaint has been to perform explant surgery, and thereafter subject the explanted material to a variety of analytical procedures in an effort to determine the cause for patient's complaint. The procedures used by pathologist are instructive in establishing an explant's appearance, and properties, as noted by a variety of microscopy evaluations. A typical sequence of process steps is shown below.

The Explant Process Steps:

1. Surgeon removes explant.

2. Surgeon immediately places the flesh imbedded mesh explant in a preservative, i.e. typically a 10% formalin solution whereupon the formaldehyde-protein "fixation chemical reaction" begins immediately. Proteins necessary for this reaction are derived from human flesh and fluids (collagen).

3. The formaldehyde reaction with protein(s) produces a crosslinked polymer that forms a shell around and adhered to the explanted mesh fibers. The newly formed polymeric shell is hard, brittle and insoluble.[33]

4. The same hard, brittle and insoluble formaldehyde-protein polymer composite encasing the PP fibers from Steps 2-3 must be removed if the PP fibers are to be properly analyzed. If the formaldehyde-protein polymer is not removed from the mesh fiber, any subsequent spectroscopic and chemical analyses are highly suspect and almost assuredly are in error. If a cleaning process is not performed, or is unsuccessful, residual formaldehyde-protein polymer will

interfere with subsequent testing and therefore make accurate and scientifically valid data interpretation difficult if not impossible.

5. Typical analyses to which I refer include: Fourier Transform Infrared spectroscopy (FTIR), light microscopy(LM), scanning electron microscopy/energy dispersive x-ray analysis (SEM/EDS), differential scanning calorimetry (DSC), thermos-gravimetric analysis (TGA), and mechanical property evaluation (toughness via tensile strength, elongation, modulus).

6. Available scientific data is collected from the conducted analyses, and expert opinions are formed and presented.

This generalized process was followed by a number of investigators cited in these matters, including Dr. Iakovlev,[34,35,36,37] Celine Mary, Clavé, Liebert, Costello, Ostergard, Rosenzweig, Klinge, etc. However, none properly considered the presence of the hard, brittle and insoluble shell of the protein-formaldehyde polymer surrounding the explanted mesh and its consequences. This well-known basic chemical reaction was "missed" by these investigators, authors, and apparently many others. As a result, significant amounts of unreliable and confusing data now permeate the media with regard to mesh explants and their propensity for surface cracking. For example, consider the manuscripts/opinions of some who have "missed" the consequences of this chemistry:

CLAVÉ

Clavé's investigation included a "sample of 100 implants explanted from patients, due to complications, was examined to evaluate the relative degradation characteristics of polypropylene (PP) and polyethylene-terephthalate (PET) prosthetics."[38] Clavé's explants, all 100, were "fixed" with formalin, and he used NaOCl exclusively with a deionized water rinse for cleaning. Our work has shown this cleaning protocol is insufficient for complete removal of "fixed" protein-formaldehyde polymers.[39,40] Clavé makes no mention of the "fixation product", and likewise does not speak to or confirm its removal prior to a series of analyses; he notes only that the "FTIR absorption bands between 1616 and 1650 cm^{-1} could be attributed either to carboxylate carbonyl or to residual products of biological origin. Therefore, these results cannot confirm the formation of carboxyl groups *in vivo*." He further disregards the absorptions in the 1600 cm^{-1} region as they are indeed of biological origin in that they are characteristic absorption frequencies for proteins. Meaning, of course, that the samples he evaluated were not completely cleaned and free of the adsorbed protein layer on the fiber surface. While the frequencies in the 1600 cm^{-1} region are diminished after cleaning, they are not absent in totality. He further writes that "The absorption band at 1730 cm^{-1} could correspond to the absorption of ester carbonyl groups, which is likely from esterified fatty acids. However, some samples of group 2 also showed that the absorption band at 1730 cm-^{1}, and they were not deemed damaged." That is absolutely what one would expect as fatty acids would not, and cannot damage Prolene or PP. Instead they serve as a plasticizer, and improve polymer physical properties.[41] Clavé continues by writing that "Additionally, FTIR analysis did not conclusively confirm that the degradation was

due to oxidation" and "None of these (hypotheses), particularly direct oxidation, could be confirmed in this study."[42] Thus, Clavé studied 100 explants and readily admits that in none of the 100 explants could he find damage due to oxidation; thus, PP was not oxidized in any of the 100 explants given his results and his conclusions. Yet, his work is frequently cited as showing that PP degrades *in vivo*. This is an example of one individual's unfounded opinion being referenced by another, and the myth propagates over and over again.

LIEBERT

Liebert and co-workers investigated extruded filaments of unmodified PP with and without antioxidants in order to determine their rate of degradation.[43] For his experiments, Liebert purchased polypropylene from Hercules and extruded it in his laboratory. Some extruded polypropylene contained antioxidants and some did not. For his antioxidant-containing sample, he used the antioxidants prescribed by an FDA approved proprietary stabilizer system. He begins his dialogue by writing that "No change in the infrared spectra or tan delta (T_g) was observed, however, for implants containing an antioxidant." He goes on to note that "Thus, it is apparent that polypropylene filaments implanted subcutaneously in hamsters degrade by an oxidation process which is retarded effectively by using an antioxidant."

Yet, even given Liebert's own admission for lack of evidence of oxidation, there are those who cite his work as proof that Ethicon's Prolene oxidizes *in vivo* (see Celine Mary).[44] It is well known and uncontested that polypropylene formulated without antioxidants are subject to oxidative degradation; however, is it equally well known that Ethicon properly protects its Prolene products with a combination of highly effective antioxidants. At the time of this writing, I have seen no scientifically sound evidence to prove Ethicon's Prolene oxidizes *in vivo*.

MARY

This investigation was conducted by a number of supporting individuals, one of which was Dr. Robert Guidoin. The article focuses on evaluating polyvinylidene fluoride (PVDF) as a substitute for Prolene.[45] The investigation utilized Prolene and PVDF sutures implanted in dogs, explanted, and "cleaned." The explants were either fixed in glutaraldehyde and post fixed with osmium tetroxide or fixed in a 10% solution of formalin. However, no data was provided to confirm complete cleaning or removal of the aldehyde-protein polymer that inextricably forms about the Prolene fibers. Furthermore, the authors state "After cleaning to remove adhering tissue, their relative biostability was assessed in terms of surface morphology and chemistry using scanning electron microscopy and Fourier transform infrared spectroscopy." However, no scientific evidence was presented to confirm complete cleaning, although the authors used surface morphology studies to establish relative biostability claims. In fact, the authors state, "The surface of the cleaned and control sutures were inspected in the scanning electron microscope to assess any surface modifications." Note that only one FTIR frequency, 1740 cm^{-1}, an absorption frequency of DLTDP, an ingredient of Prolene's formulation, was reported in this manuscript. Thus, by not having the benefit of the entire FTIR spectra, scientists reading this manuscript cannot determine if other

important FTIR frequencies are present, such as lipid esters, carboxylic acids, and proteins; all of which possess carbonyl frequencies. Such reported data, and lack of other important data, is confusing and brings a lack of clarity to this manuscript. For instance, Celine Mary and her colleagues cite the work of Liebert as "identifying" an oxidation process, chain scission, and the formation of carbonyl groups…, yet Celine Mary and her colleagues fail to include a very critical fact that Liebert did not exclusively use antioxidant stabilized PP samples. Liebert clearly states in his conclusion statement that, "Infrared Spectra and mechanical testing of implanted and non-implanted filaments containing an antioxidant show no changes in chemical or physical properties as a result of implantation."[46]

COSTELLO

First and foremost, Costello does not utilize Ethicon's Prolene in this study.[47] Secondly, the mesh materials were procured, "fixed" in formaldehyde and "cleaned" according to the following process:

"After explanting, meshes were immersed in a 10% v/v formalin solution and stored at room temperature. Prior to testing, any adherent tissue was removed from the meshes by soaking in a sodium hypochlorite solution for 2 h at 37ºC (6–14% active chlorine, Sigma Aldrich, St. Louis, MO). Each mesh was then rinsed several times with distilled water to remove any residual sodium hypochlorite solution and allowed to dry overnight."[48]

It is exceedingly important to note that Costello failed to perform FTIR analyses for chemical identification, or any other tests, to confirm complete cleaning of the protein coating residue and its removal from the explants. Thus, the fact that he relied on the hypothesis that the explants fixed in formaldehyde were completely cleaned, without any scientific evidence to affirm his tenet, does not allow serious consideration of its contents by the scientific community.

His statement, "the results from SEM, DSC, TGA, and compliance testing provided strong support that oxidative degradation was occurring *in vivo*" cannot be taken seriously given his lack of understanding of the formaldehyde-protein encased fiber.

The Costello DSC results are also suspect given no consideration to the presence of residual lipids (fatty acids), which are plasticizers and will lower the melting point.[49,50,51]

Costello, in his discussion section, makes the following statements; "The SEM micrographs displayed images of materials that were vastly different in topology than the pristine materials. The micrographs of explanted polypropylene materials exhibited cracks, surface roughness, and peeling indicative of surface degradation while the pristine materials appeared smooth."[52] Once again, conclusions are being drawn with regard to SEM micrographs of PP without any regard for the protein-formaldehyde composite formation or any scientific evidence of a truly cleaned PP surface.

Furthermore, he admittedly makes an unfair comparison between heavyweight and lightweight PP in that the lightweight PP was implanted for 5 months and its heavyweight counterpart for more than 5 years. Costello states "However, micrographs of both heavyweight polypropylene components of the explanted composite mesh (Bard product) revealed micro-cracks in the transverse directions, as well as peeling of the top layer of the fibers."[53] However, he provides absolutely no scientific data to confirm the "micro-cracks" are of PP origin. One simply cannot look at a specimen under a microscope and determine its chemical composition.

Costello, like other authors, elected to investigate the possible oxidation of PP *in vivo* yet he completely "missed" the presence of the formaldehyde-protein shell surrounding the explant fibers.

OSTERGARD

In his "Current Commentary" writings in the 2010 Obstetrics and Gynecology Journal, Ostergard states that "non-inert polypropylene degrades into potentially toxic compounds that would be expected to stimulate a greater inflammatory reaction leading to erosion."[54] He does so based solely on the Costello 2007 SEM photomicrography in Surgical Innovation.[55] He further pens a "Clinical Opinion" in the International Urogynecological Journal (2011) and cites the work of Clavé.[56,57] Ostergard presents absolutely no original scientific data to support his tenet, but only references work of others to which I have already addressed.

The Process Steps. The Process Steps described herein rely upon each individual process being conducted efficiently and effectively with appropriate chemical/biochemical consideration given each step. It is to this issue, and particularly process steps 2-4, that I raise serious concerns.

Reasons for concern and the supporting science follow:

Protein adsorption on implant device surfaces

It is well established implantation of a foreign body (mesh materials, as an example) elicits a foreign body reaction involving the immediate formation of tenaciously adsorbed and thus adhered "protein coating(s)" onto the surface of implanted material(s).[58,59,60,61] Kyriakides makes it very clear (Chapter 5 entitled Molecular Events at Tissue-Biomaterial Interface in the book *Host Response to Biomaterials*) that "Within seconds of implantation, proteins interact with the biomaterial surface and over time create a proteinaceous coating".[62] Kyriakides also states that body proteins adsorb onto implanted material surfaces and contact the surface even before cells reach the implant.[63] As a result adsorbed proteins form a coating that encapsulates the biomaterial (implant) surface before cells arrive and begin their proliferation.[64] Consequently, cells do not come in contact with the foreign object but rather with an adsorbed and adhered protein surface.

Prolene is a material to which proteins will adsorb and readily adhere.[65,66] Schmidt and co-workers state "Within milliseconds after biomaterials come in contact with a

biological fluid such as blood, proteins begin to adhere to the surface through a process known as protein adsorption." They further state, "By the time cells arrive, the foreign body material surface has been coated in a monolayer of proteins; hence, host cells do not "see" the material but "see" instead a dynamic layer of proteins.[67] Consequently, once cells finally arrive at the surface they no longer "see" the biomaterial surface itself but instead "see" a dynamic coating of adsorbed proteins." It is well understood and accepted proteins must first be adsorbed onto Prolene's surface, and thereafter "cells interact with surface proteins through direct binding to receptors on the cell membrane, but do not have receptors for a material surface alone without first contacting a coating of proteins."[68] Thus, there is no question that proteins (collagen) adsorbs onto Prolene and subsequently body cells flourish on the adsorbed proteins, resulting in encasement of the implant by a protein layer or coating. All proteins possess carbonyl groups characterized by the following chemical composition, i.e. –CONHR– or $–CONH_2$. Given these well-known precepts and an understanding of basic organic chemistry it is completely illogical for anyone to question or dispute the presence of an adsorbed-adhered protein layer on explanted Prolene surfaces. Therefore, it is equally imperative that the proteinaceous coating layer be removed from mesh material before testing mesh fibers; otherwise, an impure product is being tested and any obtained test results are unreliable. For instance, if proteins are not removed, and their presence is not known and understood, they elicit erroneous data. Consider for example light microscopy evaluations such as SEM and optical microscopy (LM). If all tissue and proteinaceous coatings (i.e. adsorbed protein) are not removed prior to fixation or immersion in formaldehyde, a high molecular weight, brittle, and insoluble, protein-formaldehyde polymer forms. The formaldehyde-protein polymer encapsulates or, in other terms, forms a shell of "armor" around mesh fibers. During this chemical "fixation" reaction, molecular contraction or shrinkage occurs. Subsequent drying of the mesh explant produces a hard, brittle protein-formaldehyde polymer encasing the Prolene fiber. This dry and hard protein coating will crack as it surrounds the explant and experiences movement.[69,70] Examples of this phenomenon have been observed during my SEM examination of explanted devices similar to the plaintiff's example depicted in Figure 8 below from a plaintiff's expert in mesh litigation.

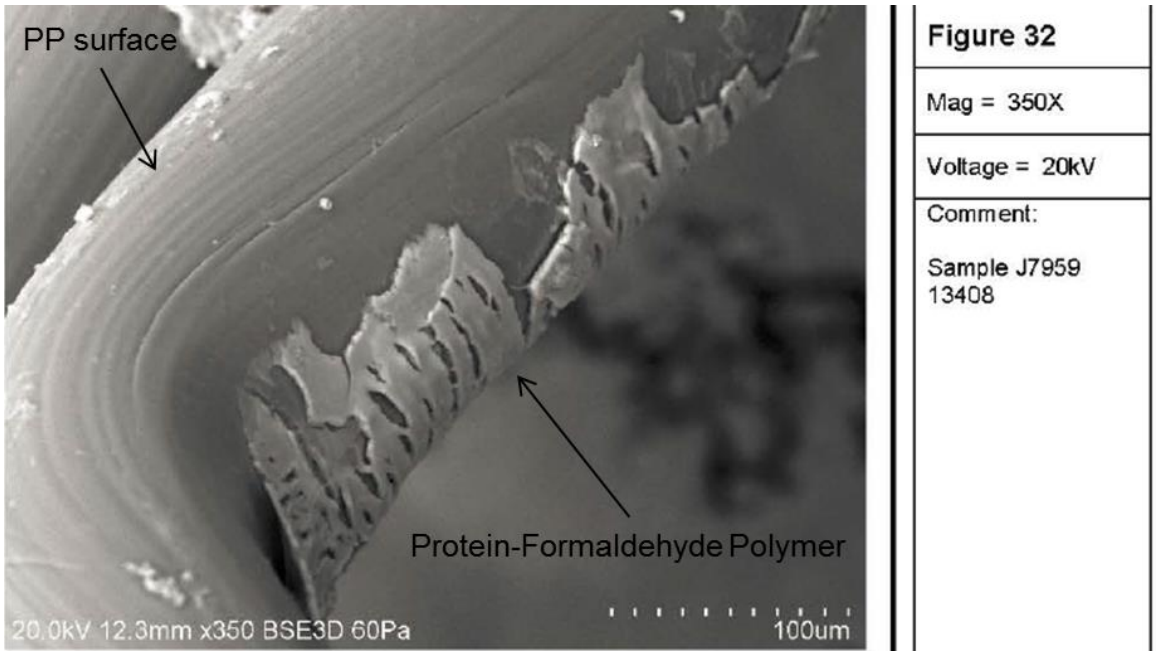


Figure 8. Example SEM micrograph taken from plaintiff's expert report in other litigation, confirming a cracked, encasing layer of protein-formaldehyde polymer.[71]

It is important to note that the surface striations or extrusion lines created during the extruding process of manufacturing Prolene fiber remain visible and unaffected after the protein coating begins to crack and fall from the fiber surface. If surface degradation of Prolene actually occurred, the extrusion lines would no longer be present.

The chemical reaction of proteins with formaldehyde is well-known, and has been for more than 60 years. The reaction of Formalin with proteins was made public in 1949 when the chemistry was first published by Heinz Fraenkel-Conrat and Dale K. Mecham.[72] It has also been well established that adsorbed protein removal from a foreign body is very difficult.[73] These authors, one of whom is Dr. Robert Guidoin, wrote "In order to study the surface chemistry of explanted prostheses, it is necessary to remove all the tissue that may have grown over and within the prosthetic structure. In the event that the explant has been treated with a fixative agent after retrieval, such as formaldehyde or glutaraldehyde, the tissue will be crosslinked and the only effective way of completely removing it is to use hydrolytic chemicals. Depending on the degree of crosslinking, strong chemicals and/or extreme hydrolysis conditions may be required."

Fraenkel-Conrat in their 1949 publication clearly described the chemical reaction transforming protein with formaldehyde into a high molecular weight, crosslinked, formaldehyde-protein polymer. The chemical reaction is shown in Figure 9.

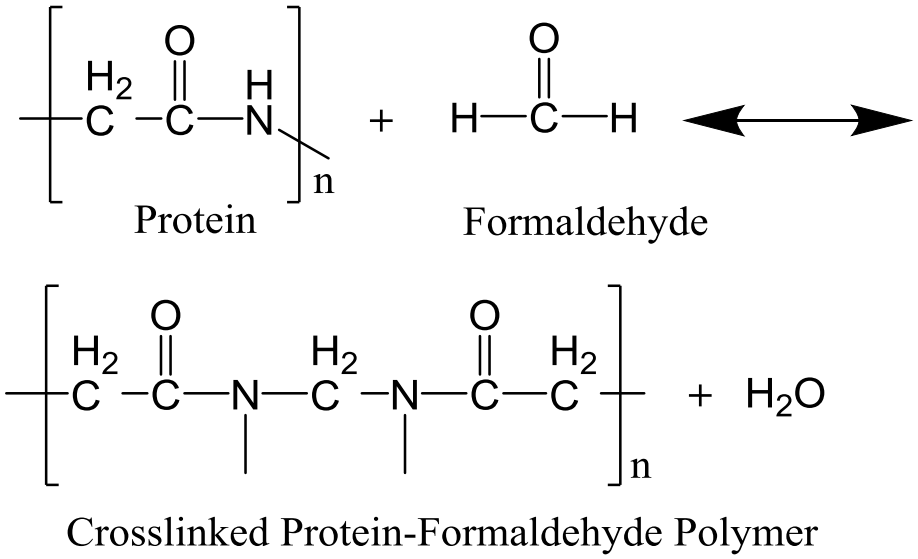


Figure 9. Reaction of protein and formaldehyde resulting in a crosslinked protein-formaldehyde polymer.

The formaldehyde-protein polymer properties are characterized by:[74,75]

- Insolubility
- Brittleness
- Hardness
- Contains at minimum, Carbon, Hydrogen, Oxygen, Nitrogen

The authors' 1949 manuscript stated "Preceding papers from this Laboratory have shown that at room temperature, and within the range of pH 3 to 9, methylene crosslinks can be formed between amino groups on the one hand and amide, guanidyl, indole, phenol, or imidazole groups on the other."[76] Numerous papers have since been written reaffirming what is a very well-known protein-formaldehyde crosslinking reaction.[77,78,79] In fact, Dr. Susan Lester has prepared a Manual of Surgical Pathology, 3rd Edition, copyrighted in 2000, 2006, and 2010 describing the fixation process.[80]

In support of Fraenkel-Conrat, *et al.*, Fox and co-workers wrote in the 1985 Journal of Histochemistry and Cytochemistry, and described formaldehyde as a tissue fixation chemical.[81] These authors brought attention to the work of Ferdinand Blum who, as early as the 1980's, was responsible for several articles on the reactions of formaldehyde as a "tissue fixation" agent. Fox, *et al.* reported when tissue is placed in formalin, "A major concern in fixation by formaldehyde, or with any fixative, is the amount of distortion produced by the fixation process. The usual term applied to fixation distortion is shrinkage."[82] These authors also note "A variety of concentrations of formaldehyde were tested for use as a fixative for electron microscopy, but no

concentration of formaldehyde between 0.5 and 20% produced photomicrographs comparable with those from glutaraldehyde fixed tissues."[83]

Lester, likewise, has written that "most fixatives cause shrinkage of the tissue and offers additional information regarding formalin as a fixative."[84] Dr. Lester in the text titled "Manual of Surgical Pathology"[85] writes:

1. If exact measurements are important, they should be taken prior to fixation.

2. Unbuffered Formalin degrades rapidly. Composition: 10% phosphate-buffered Formalin (Formalin is 40% formaldehyde) in water, does not preserve nucleic acids well.

3. Formalin is the standard fixative of most pathology departments and has been used in many studies of special stains and immunohistochemistry. It fixes most tissues well and is compatible with most histologic stains.

4. Tissue can be preserved in formalin for many months. Fixation occurs due to crosslinking of proteins.

5. Crosslinking occurs over time; therefore even small specimens (e.g., core needle biopsies) need to "fix" for a minimum of 6 to 8 hours

6. Formaldehyde, a highly reactive chemical and polar reagent, can function as an extraction solvent and/or chemically react with other non-protein chemicals, i.e. "Lipids and carbohydrates are often lost during processing unless special techniques are used."

In the review *Crosslinking fixatives: what they are, what they do, and why we use them,* the authors discuss formaldehyde and its preference for reacting with proteins during the fixation process.[86] These concepts are illustrated in Figure 10.

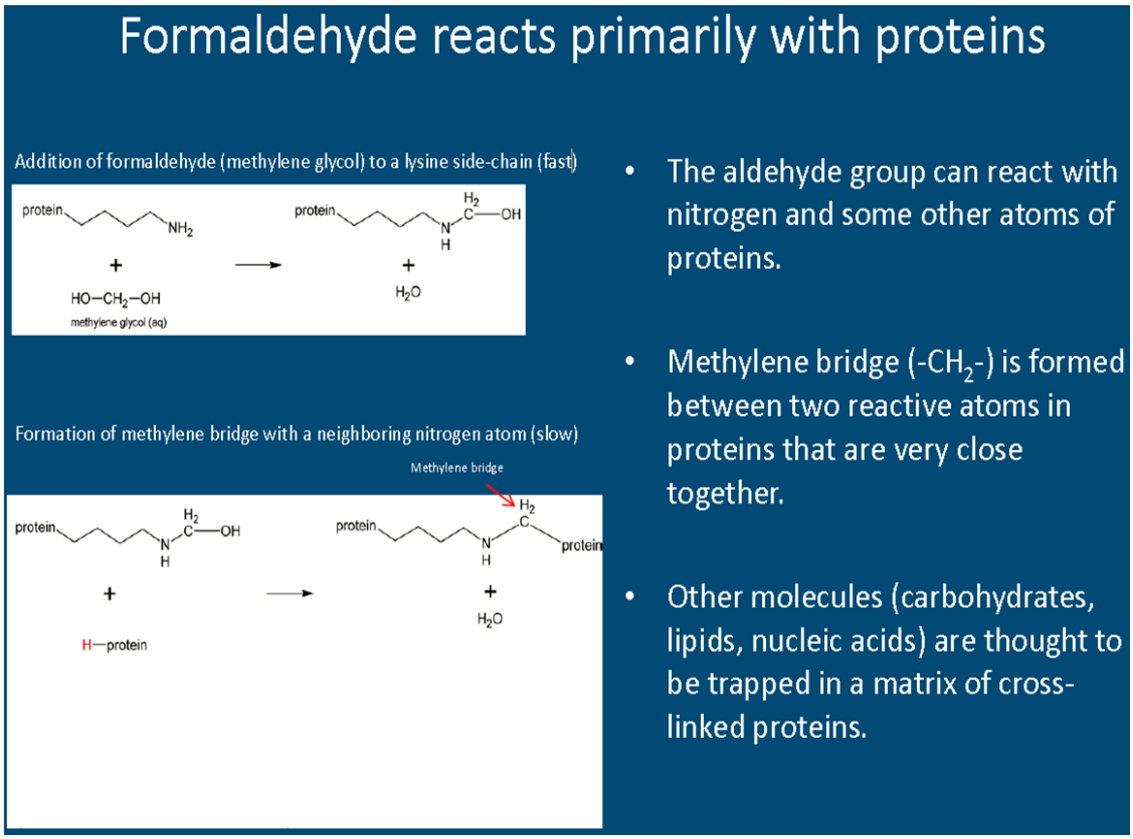
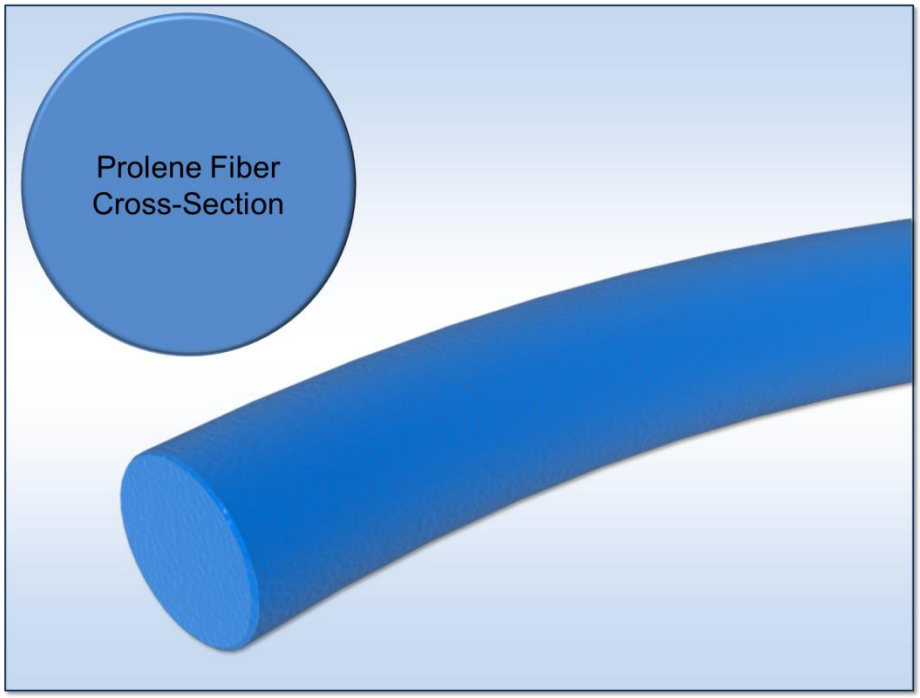


Figure 10. Formaldehyde reactions with proteins during the fixation process.[87]

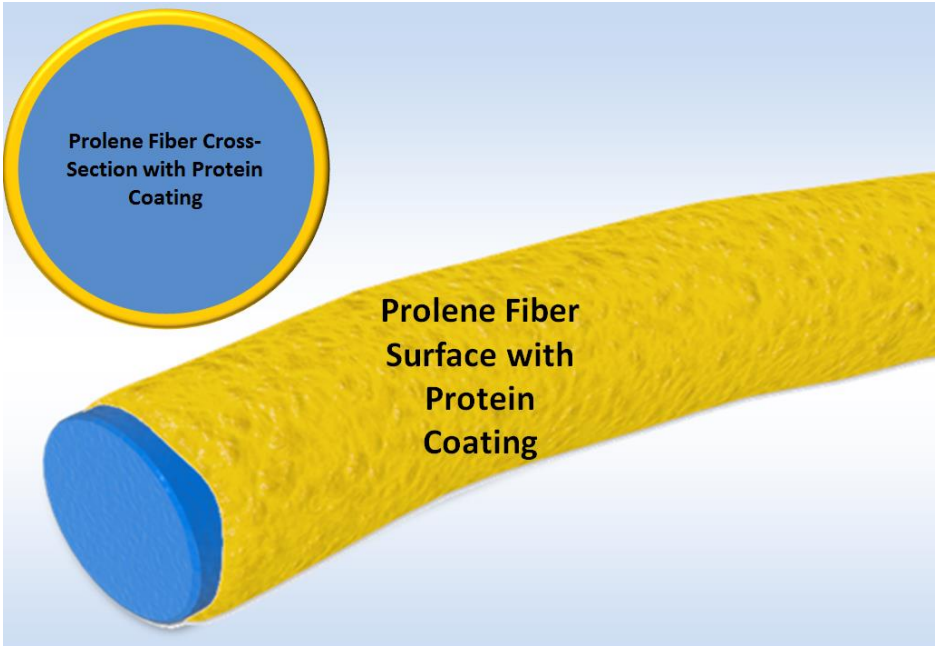
In summary, the well-known reaction of proteins and formaldehyde produces a hard, brittle, insoluble crosslinked polymer that defines the basis of flesh "fixation" long known and used by histologists and pathologists. However, as noted, the formaldehyde-protein polymer is extremely difficult to remove from mesh fibers. Therefore, interpretation of much of the printed analytical data derived from formalin-treated explants is suspect and, frankly, unreliable unless special consideration is given its presence and chemical reactivity as well as an appropriate cleaning protocol.

Figure 11 illustrates the protein-formaldehyde encapsulation of Prolene fibers and subsequent cracking of the protein-formaldehyde shell surrounding the fibers.

a) A pristine Prolene fiber used in Ethicon's mesh.



b) After the pristine, Prolene mesh is implanted, within milliseconds protein coatings immediately form around and through the mesh.[88]



c) The Explanted Mesh with protein coating attached is placed in a Formalin (formaldehyde) solution. The Formaldehyde-Protein Fixation Chemical

Reaction begins and continues for as long as the mesh is in formalin. The formed and crosslinked adsorbed protein coating is brittle, insoluble and hard. The brittle and hard Prolene casing will crack with drying and/or physical manipulation.

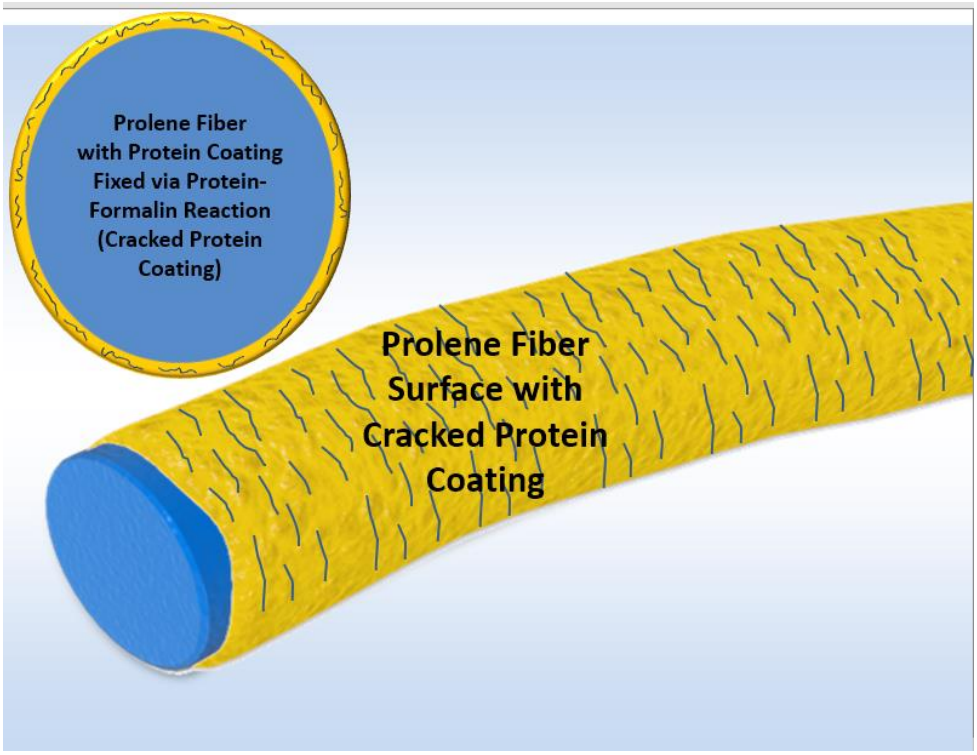


Figure 11. Protein-formaldehyde encapsulation of Prolene fibers and subsequent cracking of the crosslinked protein-formaldehyde shell.

The writings of others, as noted by Iakovlev[89], including but not limited to the work of Costello *et al*.[90], have claimed, without definitive scientific evidence, that explanted PP degraded to the extent its intended use has been compromised. For instance, Costello boldly concluded that "…explanted PP meshes did undergo degradation while *in vivo*…" Clavé further clouds the issue of PP stability with his manuscript titled "*Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants*".[91] Costello's statements are misleading in that he had no analytical data supportive of his conclusion, which was "The studies provide evidence contrary to published literature characterizing PP as inert in such applications." Furthermore, Clavé purports to perform DSC to identify *in vivo* changes or "degradation" of PP via changes in glass transition temperature (T_g), melting temperature, and heat of fusion. However, he goes on to report DSC thermograms of what he referred to as treated, degraded, and non-degraded LDPPMF (low density polypropylene multi-filament) explants were all similar to treated pristine Prolene. Additionally, his experimental evidence via DSC thermograms of so-called "degraded" and non-degraded HDPPMF (high density polypropylene multi-filament) explants were reported as being similar to those of the treated, pristine, Prolene samples.[92] It is inconsistent with scientific principles for Clavé to suggest that degraded, non-degraded, and pristine Prolene all possess similar DSC thermograms.

There would be definable and explainable differences in these very important polymer properties had PP degradation occurred. Furthermore, he states that no modifications were observed in the melting temperature or heat of fusion of these samples. However, the presence of structural modifications (i.e. degradation) or material impurities, if they exist, (i.e. presence of degradation products) will alter melting point and heat of fusion values.[93] Clavé writes that, "Thus, if oxidation occurs in these prosthetics, it takes place in the amorphous zones, and crystallinity is preserved."[94] However, there is no scientific evidence that oxidation of Prolene occurs.

FTIR Data

The use of Fourier Transform Infrared (FTIR) spectroscopy is, for the most part, an analytical tool of qualitative analysis. In the following discussion, I will focus on frequency assignments as they relate to functional groups such as carbonyl groups (C=O). It should be noted that the strong frequencies at 1539, 1653, and 3300 cm^{-1} are indicative of protein(s) and not PP and/or Prolene.[95] In lay terms, each molecular species possesses an FTIR absorption unique to that molecule; much like finger prints of humans.[96] Each human is said to possess a unique finger print, and thus the reason finger print data is used extensively to determine human identification. However, in identifying molecular species or chemical structures via infra-red spectroscopy, it is necessary to establish the "fingerprint" for the molecules to be studied; just like it is necessary to take a human's finger print and store data in a file for subsequent "matching" should the need arise. The presence of absorption frequencies, as well as the absence of same, are instructive in confirming sample identification. For instance, the FTIR spectrum of pristine Prolene has no carbonyl group and thus is absent the strong carbonyl frequency, while proteins, possess a strong carbonyl frequency. Both represent structurally different characteristic features of dissimilar chemical species, proteins and Prolene.

Other plaintiff's experts have often made no effort to remove adsorbed protein from explanted samples prior to evaluation. Thus proteins would be expected to be present on the explant samples. It is instructive to remember that all explant samples discussed herein were "fixed" in formaldehyde.

One must then ask the question, if proof for oxidation of Prolene is the presence of carbonyl bands or frequencies, accompanied by loss of molecular weight, how can one knowledge in the field continue to espouse oxidation when no carbonyl band exists and molecular weight loss has not occurred?

Consider the following; carbonyl bands are structural entities possessing carbon and oxygen (C=O) and are indicative of oxidation when they form from a molecule made of only carbon and hydrogen, as is PP. Stuart states in her text, "Carbonyl stretching is one of the easiest absorptions to recognize in an infrared spectrum." It is usually the most intense band in the spectrum, and depending on the type of C=O bond, occurs in the 1830 – 1650 cm^{-1} region."[97] Indeed, my experience as a scientist has shown that to be true. By way of example, examine the Reference Spectrum (Figure 12) for Polypropylene[98] and then for oxidized polypropylene (Figure 13).[99] PP does not

possess a carbonyl absorption frequency as it is a molecule made of only carbon and hydrogen. Accordingly, there is no carbonyl frequency in Figure 12. However, Figure 13 is another matter, as this spectrum represents oxidized PP, wherein a carbonyl frequency is predicted to be present, and it is; see the 1740 cm^{-1} frequency.

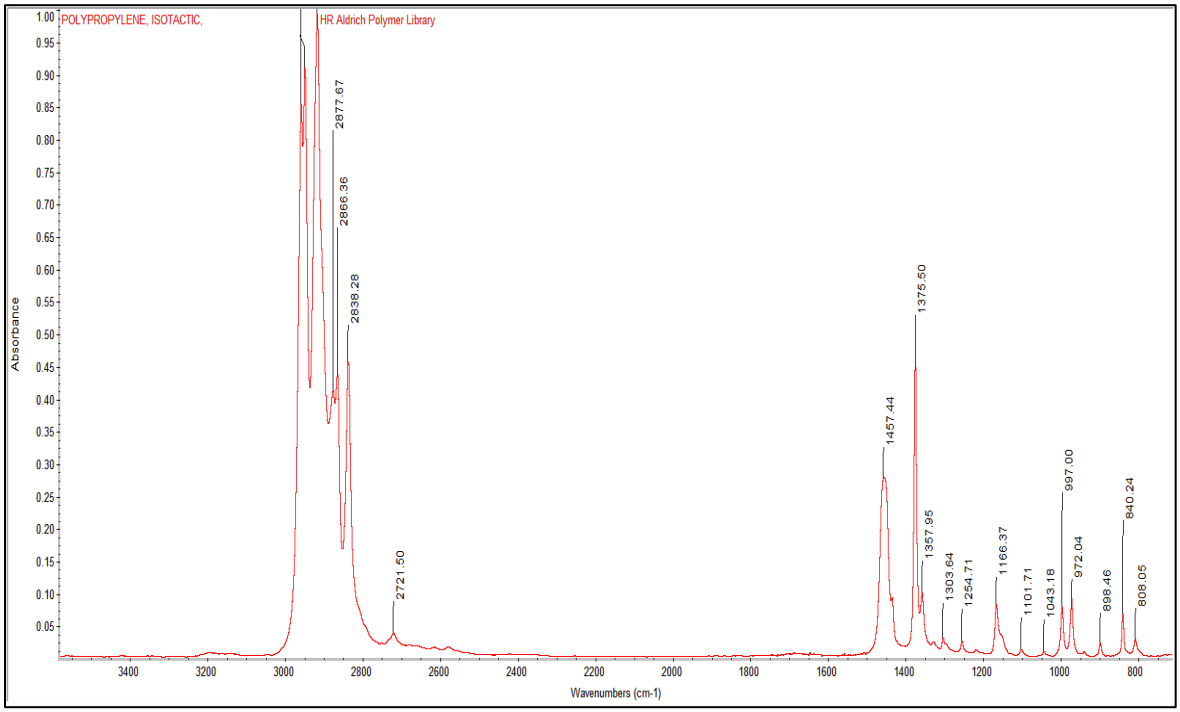


Figure 12. Reference Spectrum of Isotactic Polypropylene, HR Aldrich Polymer Library.[100]

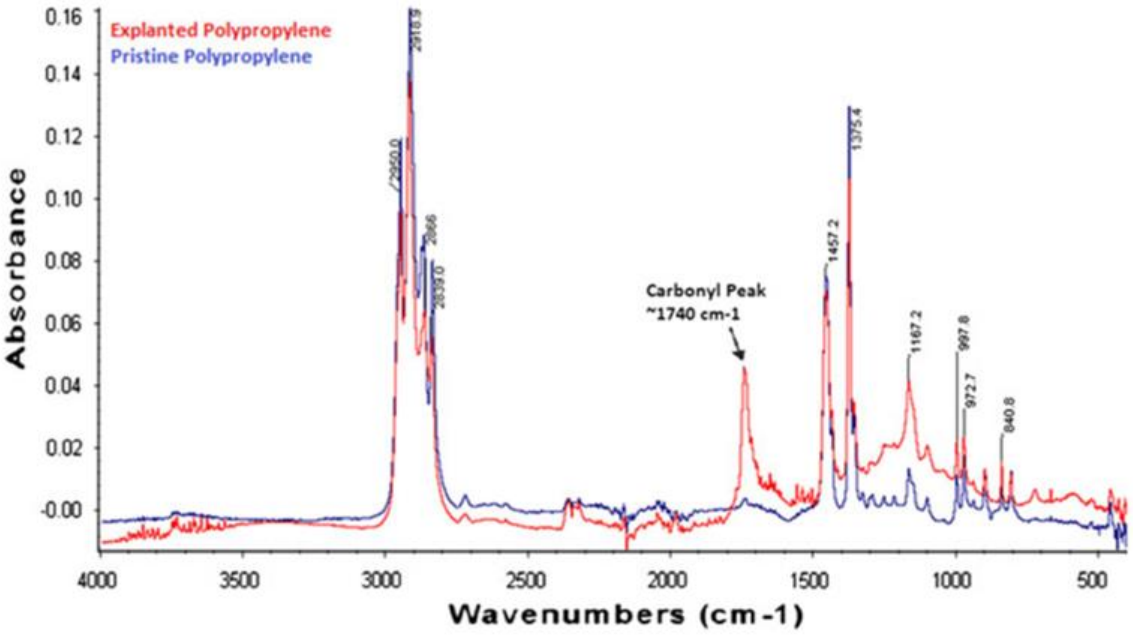


Figure 13. Referenced Spectra for Oxidized Polypropylene via Wood, *et al.*[101]

The Wood, *et al*. manuscript includes a spectrum of oxidized PP represented by a strong carbonyl, as specified by Stuart, frequency at 1740 cm^{-1}.[102] It is important to note that the sample in the spectra is **not** of an Ethicon device and reportedly does not contain an antioxidant additive package.[103] It is imperative, however, that proteins possess carbonyl groups, in the form of the amide functionality (Figure 14), and amide carbonyls strongly absorb light, as they should. Figure 15 details the characteristic infrared bands of peptide linkages[104] while Figure 16 displays the FTIR spectra of collagenase, a human protein.[105]

In summary, I have not observed any FTIR data or evidence of Prolene being oxidized while implanted.

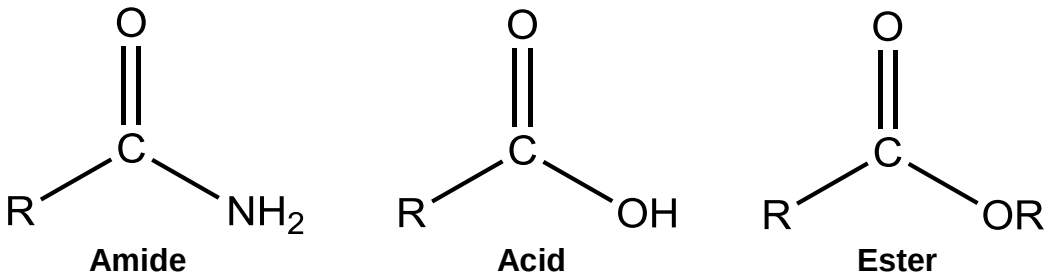


Figure 14. General structures of an Amide, Acid, and Ester

Table 1	Characteristic infrared bands of peptide linkage	
Designation	Approximate frequency (cm^{-1})	Description
Amide A	3300	NH stretching
Amide B	3100	NH stretching
Amide I	1600–1690	C=O stretching
Amide II	1480–1575	CN stretching, NH bending
Amide III	1229–1301	CN stretching, NH bending
Amide IV	625–767	OCN bending
Amide V	640–800	Out-of-plane NH bending
Amide VI	537–606	Out-of-plane C=O bending
Amide VII	200	Skeletal torsion

Figure 15. Characteristic Infrared Bands of Peptide Linkage[106]

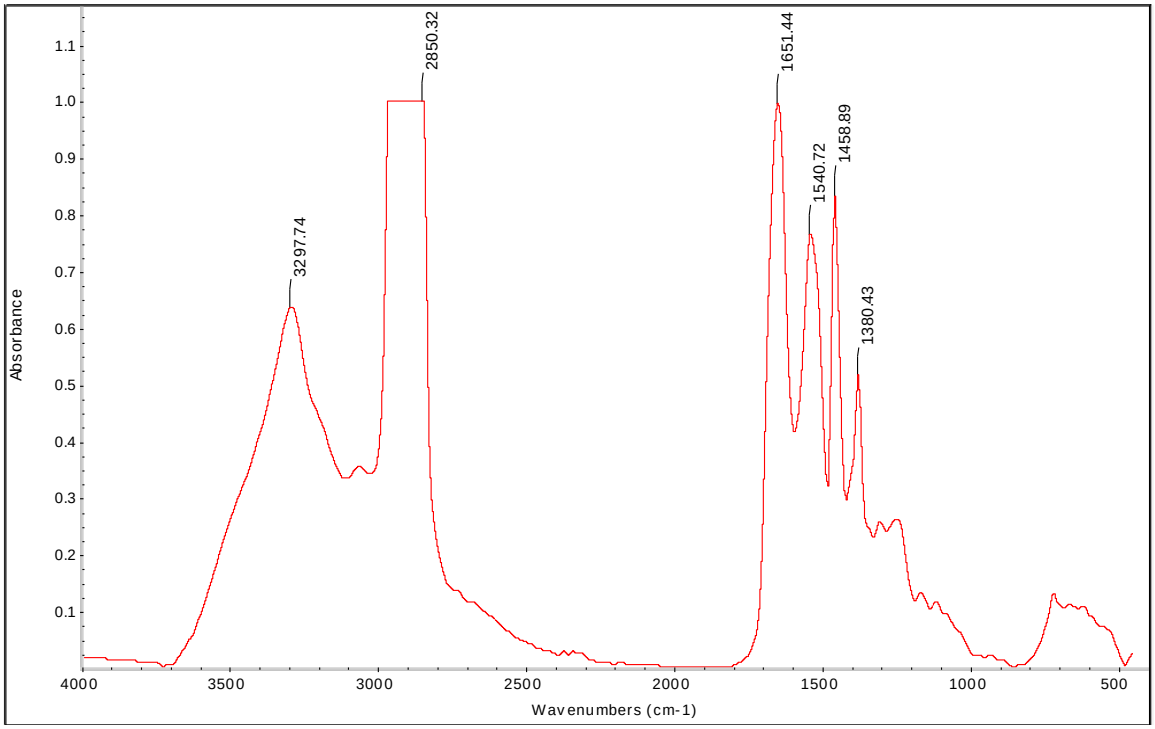


Figure 16. Collagenase (Sigma Biological Sample Library)[107]

Consider the issue of "oxidation of polypropylene." Polypropylene, and also Prolene, can oxidize under the right conditions, i.e. in ultraviolet light; a circumstance we are not dealing with in the matter at hand. Testing and analyses data are presented herein to scientifically and conclusively prove Prolene did not oxidize in the conditions present in this matter. When speaking of polypropylene oxidation, it is not unusual to note thermal condition requirements well above 150ºC (302ºF).[108] The normal body temperature is a mere 37ºC or 98.6ºF and insufficient to affect PP thermal degradation.[109] Prolene does not begin to oxidize or degrade until a temperature of 333ºC or 631ºF is reached as demonstrated by TGA analysis shown earlier in this report (Figure 4). Polypropylene, and also Prolene, exhibit excellent thermal stability well above body temperature.

Hydrolysis

Hydrolysis is a mechanism for molecular weight reduction of hetero-polymers, but not in the case of Prolene or polypropylene; PP is a non-hetero polymer.[110] Polypropylene is composed of main-chain, carbon-carbon atoms and it is absolutely not susceptible to hydrolysis.[111] Polypropylene's main chain carbon atoms are not polar and consequently do not attract attack by polar groups such as water. Since hydrolysis is defined as breaking apart by water and water is not attracted to PP, hydrolysis of PP does not occur. In lay terms, PP and water do not like each other at the molecular level. In fact, PP and Prolene are highly resistant to water and water vapor as already noted in this report.

Environmental Stress Cracking

Environmental Stress Cracking (ESC), as claimed by other plaintiff's experts is not cause for polypropylene degradation. Fred Billmeyer, in his Textbook of Polymer Science, page 388, states "PP …is completely free from environmental stress cracking."[112] Others have also reported PP's well-known high resistance to ESC.[113,114] The authors state "It should be noted, however, that PP has excellent resistance to ESC."[115,116] They also write that "fracture of material, which is accelerated by the environment, requires crack initiation in the crazed region and subsequent fast crack propagation, and therefore a brittle failure mode" (page 206).[117] References to the work of Maier and Calafut[118] have been made by other plaintiff's experts, yet they fail to mention the treatise statements on ESC of Polypropylene. The following quotes are taken from Calfut's document; "Environmental stress cracking emerges as the most prominent cause of failure in all plastics. For polypropylene, this problem can be disregarded. "A major advantage of the material is its apparently complete resistance to environmental stress cracking,"[119] and "One of the major advantages of polypropylene is its apparently complete resistance to attack by environmental stress cracking."[120]

As confirmed by my work, the explant surface (adsorbed proteinaceous matter, not polypropylene) shows cracks perpendicular to, and not oriented with the tensile stress direction. Thus, the Prolene fibers in this matter do not meet the criteria for crazing nor ESC. ESC has requirements of "crack initiation in crazed region and subsequent fast propagation,"[121] neither of which has been witnessed in my work.

Neither Prolene nor PP undergo Environmental Stress Cracking.[122] Also, it is well established that fatty acids, fatty acid esters, and similar chemicals plasticize PP and improve its toughness.[123,124] D. Tripathi in Practical Guide to Polypropylene states "PP is virtually free from environmental stress cracking (ESC) observed in other polymers and attempts in the laboratory to identify a pure ESC agent for PP have failed. Many plastics are inclined to ESC or embrittlement on prolonged contact with boiling detergent solutions. The PP components specially made for washing machines do not exhibit these disadvantages. A reflux test involving 1000 hours in boiling detergent solution is used to measure water absorption, embrittling, and change of the dimension. It has been reported that suitable grades show 0.5% higher water absorption than the normal grades when soaked in detergent solution. Furthermore, no embrittlement is observed and the yield stress, ultimate tensile strength, dimensions, surface hardness, rigidity and toughness of PP are not changed."[125]

There is no evidence to support ESC in any explants that I have examined or for PP for that matter. ESC, if it occurred, would dictate fiber rupture, loss in tensile strength, loss of elongation, loss in toughness, and loss in molecular weight, all of which are unsupported by scientific evidence/data.

Molecular weight and degradation

The work of Wypych, in the **Handbook of Material Weathering**, made it perfectly clear that oxidation of PP is accompanied by an increase in carbonyl concentration and an accompanying decrease in molecular weight, due to "chain scission" in surface layers.[126] The two effects simply follow each other, one cannot happen without the other happening. Supporting this tenet is the work of Zweifel, *et al.* in the **Plastic Additives Handbook** who summarized changes in material properties during polymer aging, i.e. as degradation occurs, mechanical failures increase, molecular weight changes, molecular weight distribution changes, carbonyl increases occur, along with a rapid increase in hydroperoxide formation and a fast oxygen uptake.[127] They identify "the most important propagation reaction leading to chain scission of the macromolecule is the so-called beta-scission reaction of the alkoxy radical." This reaction, of course, leads to extensive carbonyl formation.

Fayolle, *et al*., in "Polymer Degradation and Stability, 2000 wrote in the manuscript titled Oxidation induced embrittlement in polypropylene - a tensile testing study that PP "embrittlement occurs at a very low conversion of the chain scission process (only 1 scission per 3 initial chains) and it can be demonstrated that it results from a decrease in polymer toughness."[128] The 7-year dog study of Burkley confirmed, without doubt, that polymer toughness did not decrease, but instead improved with implantation. Clearly, given this referenced laboratory 7-year study, one cannot scientifically question the issue of Prolene's *in vivo* stability.

Yakimets, *et al*. in Elsevier's Journal Polymer Degradation and Stability, 86 (2004), pages 59-67 studied the "Effect of photo-oxidation cracks on behavior of thick polypropylene samples."[129] They found that "this kind of aging generally leads to an embrittlement of polymer materials. It causes a dramatic effect on the mechanical properties and fracture behaviour" as noted if Figure 17 below. None of which has been confirmed for Prolene.

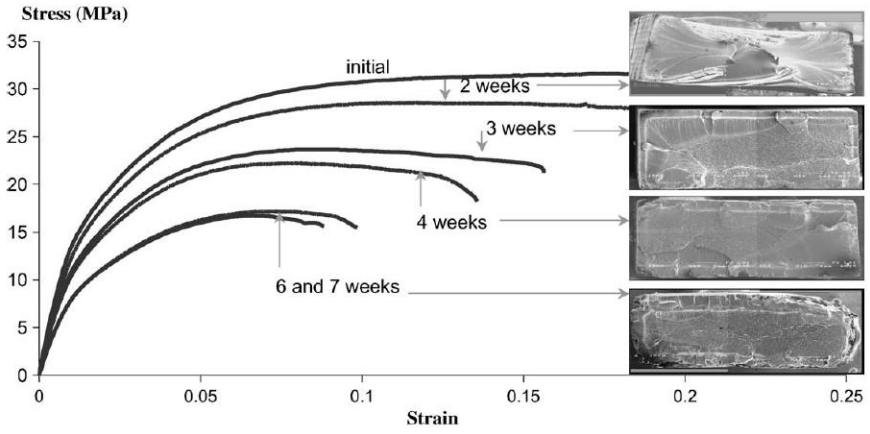


Figure 17. Stress-strain plot as a function of aging time.[130]

Scheirs writes in Compositional Failure Analysis of Polymers; a practical approach that polymer oxidation leads to loss in molecular weight and subsequent embrittlement/cracking.[131] No one, to my knowledge, has shown any meaningful changes in Prolene molecular weight during implantation.

Thus, it can be stated to a reasonable degree of scientific certainty that the Prolene sutures did not degrade in the 7-year dog study.

I have reviewed molecular weight analysis of more than 20 samples characterized via high-temperature GPC (HT-GPC). These analysis and molecular weight data were reported by plaintiffs' expert, Dr. Howard Jordi, and I rely on the results included in his Final Report of May 20, 2014. Dr. Jordi states on page 6 that "oxidative degradation can alter its molecular weight and polydispersity index (PDI) through cleavage of the long polypropylene chains into smaller fragments."[132] It is instructive, however, that his reported data does not support loss of molecular weight during implantation.

The Jordi report has listed depolymerization as a means of oxidizing or reducing the molecular weight of polypropylene. Depolymerization, by the very context of the word, de-polymerization, is the opposite of polymerization. The former reduced the molecular weight while the latter increases molecular weight. Indeed, if depolymerization occurs in the TVT products or any other polymeric products, a loss in molecular weight will occur. Quite simply, the original molecule will become smaller, and weigh less, because its polymer chain was broken into two or more smaller, individual molecules.

Gahleitner and Feibig write that "In contrast to other polyolefins, such as PE (polyethylene) or most olefin-elastomers (EPR, ethylene propylene diene rubber (EPDM), radical reactions in PP cause mainly a degradation effect, reducing the average chain length of the polymer and especially affecting the high molecular weight fraction---a significant reduction of mechanical properties can be expected. The normal consequence is embrittlement, a massive decrease in toughness."[133] Therefore, if there is oxidation or other degradation forces upon Prolene mesh fibers causing molecular weight loss, it is clear and obvious reduction in molecular weight will adversely affect physical properties of the TVT products or, for that matter, any polymeric product. Consider the facts/data, however, where in the current matter it was shown by two investigators, Daniel F. Burkley, an Ethicon employee, and Dr. Howard Jordi, founder of Jordi Labs and plaintiff's expert, that molecular weight changes did not occur *in vivo. Thus*, there was no Prolene degradation. Furthermore, the excellent physical properties obtained by Burkley, from the explanted sutures of his 7 year dog study, is consistent with no loss in molecular weight of Prolene, and is additional data confirming Prolene does not degrade *in-vivo*.

In Burkley's study, wherein he selected six samples from four dogs, there were no significant changes in molecular weight for any of the polypropylene suture materials after 7 years of implantation.[134,135] Furthermore, Dr. Jordi performed molecular weight determinations on TVT products; both pristine TVT and explanted devices from Carolyn Lewis and Linda Batiste. Like Burkley, Dr. Jordi, in the Jordi Final Report, wrote "The Jordi GPC analysis of both control and explant samples tend to confirm "The 7 year Dog Study" performed at Ethicon referred to as Exhibit T-2182 in his (Burkley's) deposition of May 22, 2013, in that little to no macro Mw degradation was noted."[136] In other words, both Burkley and Jordi independently determined unequivocally that Prolene does not degrade (no MW loss) *in vivo*. Therefore, no degradation of Prolene occurs in-vivo, as molecular weight loss is a form of degradation, i.e. no degradation, no molecular weight loss.

Microcracking and related studies

I have received a number of documents dealing with alleged Prolene "cracking" and circumstances surrounding this supposed phenomenon as suggested by plaintiff's experts and others. Accordingly, I will discuss a number of these documents below:

1. ETH.MESH 12831405 June 15, 1982 memorandum discussed cardiovascular and ophthalmic implants. Crack depths were measured but lack of precision was evident with a stated +/- 50% estimate of depth for the ophthalmic implants. Edge on views of cracks for the cardiovascular explants varied from 2 to 4.5 microns. There was no study or effort to identity the cracked material. The depth of cracks and the measurement precision noted above contributes little to the issue. Thus, with no identity of the composition of the cracked area the data has little significance to the topic at hand.

2. ETH.MESH 00006313-6314 by Emil Brysko, Ph.D. titled "Examination of 5/0 and 6/0 Cardiovascular Prolene Sutures Explanted after 2 to 6 years Implantation" was reviewed. This study used 9 explants, 3 were stored wet in Formalin and 6 were allowed to dry and were evaluated dry. No tissue was removed from any of the explants.

Wet samples were evaluated for cracking, then allowed to dry and reexamined. It is significant, but not surprising, that wet samples at 2, 3, and 6 years were essentially crack-free. The 3 year sample was reported to have "barely visible cracks in small area."

Two of the dried and three two year explants exhibited cracks while one had no cracks.

A dry, 4 yr. explant was cracked; and two of the three year dried explants were cracked while the wet 3 year implant was not cracked.

Finally, the 5.5 yr. dried explant was cracked, as was two dried 6 year explants. However, the remaining wet six year explant was not cracked. The conclusion was that "sutures kept in the wet state do not crack."

It was also stated that a wet, non-cracked sample was observed to begin to crack while it was drying. This observation involved a non-cracked, wet explant being placed on a microscope stage and "cracking was actually observed by drying." These data are totally consistent with the tenet that cracked material noted by SEM and OM is not Prolene but rather tissue and or protein-formaldehyde polymer formed during the flesh "fixation" process. For instance Prolene is hydrophobic, as it is 100 percent hydrocarbon and hydrocarbons do not "like" or dissolve in water. Thus, Prolene does not absorb water, and nor does it swell in

water to the extent it would crack during a drying off process. The material cracking upon drying is clearly hydrophilic, and when wet, imbibes water and swells. When the drying process begins the tissue/protein-formaldehyde polymer contracts during water loss, becomes brittle and cracking ensues. Hydrophobic Prolene would not, and cannot by its chemical composition, react to the presence of water loss as described.

3. ETH.MESH 00006309 BY Matlaga, Sheffield, and Fetter on May 25, 1983 described the evaluation of an explant suture obtained from Dr. Gregory. The explant was a Prolene vascular graft fixed in formalin. The explant was removed after 3.8 yrs. implantation time, and kept in formalin for approximately 6 weeks prior to analyses. Three of the explanted suture samples were subjected to tensile strength measurement with an 80% retention of tensile strength value compared to a control suture. This is not surprising given the Burkley study showed a decrease in tensile strength after implantation but with increases in elongation, a physical property manifestation leading to an increase in suture toughness with implantation time. Matalaga, *et al*. did not report elongation values. Thus, while a portion of the data as reported is consistent with the Burkley study, it is insufficient to be meaningful in arriving at a final conclusion regarding physical properties of the explanted Prolene.

4. ETH.MESH 00006312 of Nov. 7, 1984 investigated the status of a 7 year ophthalmological explant. The memorandum speaks to wet and dry states so it is unclear as to whether the explant was received wet or was dry and tested wet. It is therefore difficult to draw any conclusion from these data regarding origin of cracking, if same existed.

5. ETH.MESH00006310 by Franklin Schiller on Sept. 27, 1984 reports on a Prolene suture removed from an eye after 7 years implantation. The explant was fixed in glutaraldehyde and thus the protein-aldehyde fixation reaction took place. The sample, with no noted cleaning, was viewed by SEM where cracking was observed over most of the suture surface. Given the fixation process and lack of explant cleaning, the reported result is not surprising.

6. ETH.MESH 00006386, a November 5, 1984 memorandum titled “Prolene Microcracking” reported on sutures from ophthalmic as well as cardiovascular applications. Unfortunately there is no information on the method of fixation for any for these explants. What is interesting, however, is the statement “In severe cases, the cracks lead to the production of a separated layer of seemingly uniform thickness and a relatively clean surface underneath.” These observations strongly suggests fixation in formaldehyde with subsequent protein-formaldehyde polymer formation, and thus the uniform thickness and a relatively clean surface (Prolene) underneath. It is significant two distinct layers were noted, “a separated layer,” and a “relatively clean surface underneath.” If the viewed surfaces were Prolene in

origin, there would not have been a driving force for two distinct layers, as they would have been material of like composition.

7. ETH.MESH 00006304 study titled "Fourier Transform-Infrared Examination of Prolene Microcrack and Photo-Oxidized Polypropylene" dated November 13, 1984 reported three methods of infrared examination and they were: 1. ATR surface examination, 2. Examination of explants on micron level with FTIR-microscopy, 3. Examination of photo-oxidized Prolene films via FTIR.

The study intent was to determine the composition of the exterior surface of cracked explants, and if treating explants with formalin for storage and attempted removal by toluene produced artifacts in the ATR-FTIR results. Explants 83-165 and 84-194 were examined. It is unclear whether these explants were fixed in formalin but without a statement to the contrary, suggests they were. The authors note "clear evidence of protein was observed at 1660 and 1540 cm-1 and a band at 1714 cm-1which the authors assigned to oxidized Prolene. With respect to the latter assignment, I disagree. This is the lipid or fat carbonyl absorption region.[137] Sakoda states "The extent of oxidation is usually measured by FTIR spectroscopy. However, there could be considerable error in the measurement since it is difficult to distinguish the peak derived from lipids adsorbed in UHMWPE from that from oxidation of UHMWPE."[138]

The FTIR spectra to which they refer are not available to me at this time but I am aware that the 1714 cm^{-1}region is not a protein carbonyl but an ester (lipid) or fatty acid region absorption. It is not clear why explant examination would be conducted by ATR-FTIR and serum protein would be annealed at 125^{o}C and deposited on NaCl plates for transmission FTIR, a change in obtaining FTIR spectra. Such reaction conditions are very likely to hydrolyze protein amide bonds with transformation to an ester or carboxylic acid and thus create the presence of the 1714 cm^{-1} absorption, an absorption not originally in the explant. Also, it is unclear what the author means by "ATR spectra of clean Prolene."

8. The ETH.MESH 00006325 of Dr. Peter Moy's March 11, 1985 memo and entitled "Prolene Microcrack Experiments" comments that given the many studies to understand the supposed "cracking" of PP explants, "only two explanted sutures have been examined in greater than cursory detail." In his attached data it was noted that aorta and heart explants *in vivo* from 1-4 years and stored in formalin had no cracks, while a vascular graft implanted for 2 years with unknown treatment showed no cracks, a 2 year vascular explant showed no cracks when wet, but during drying cracking became apparent. Abdominal explants from 3-5 years implantation and stored in formalin showed no cracking on histology slides, while a 3 year vascular graft explant stored in formalin showed some cracking. Similar results were noted for other explants with the predominance of cracking accompanied by formalin fixation.

ACC. No. 83-165, a vascular graft, implanted for 6 years and stored in formalin after explanting, provided interesting and instructive data. For instance, the formalin treated Prolene sample showed surface cracking. However, when the explant was examined wet, no cracks were evident but when the sample was dried, cracks were evident. Surface flakes were examined by FTIR and only proteins and Prolene were present and no oxidized species.

On September 30, 1987 Dan Burkley submitted a report ETH.MESH 12831391 titled “IR Microscopy of Explanted Prolene Received from Professor R. Guidoin.”

Samples were examined “as is” with no special preparation. He wrote “the IR spectra appeared bottomed out since the sample thickness is quite significant.” This type spectral interference accompanies transmission microscopy as the incident light must travel through the sample. The thicker the sample, the poorer spectral resolution.

Burkley noted the Guidoin sample 83D035 implanted for 8 years was examined optically. The explant was scraped with a needle to obtain a waxy snow which was not conducive to FTIR spectroscopy in that form. The sample melted at 147-156 °C and stated this was the melting point range previously observed for oxidatively degraded PP. However, no data was provided to confirm how the melting point of “oxidatively degraded PP” was determined. For instance, it is well known that presence of impurities cause melting point depressions.[4] It is obvious from Fig. 10-11 that proteins are present after spectral features of moisture are subtracted, leaving Prolene and proteins with possible carboxylate ester or acid frequencies present. Burkley is clear that the 1718 cm^{-1} absorption is “a carbonyl band most likely with esters but also likely with acids.” He is correct in that the 1718 cm^{-1} frequency could as well be from calcium stearate, the flow control agent making up part of Ethicon’s Prolene formulation. The 1638 cm^{-1} frequency is assigned as Amide 1 and 1618 nucleic acids or lipid absorptions. Thus, a melting point depression described by Burkley can be the result of impurities to Prolene such as those described.

Finally, I disagree with the Burkley conclusions[139] given the following:

- There is insufficient analytical data to determine if Dilauryl Thiodipropionate (DLTDP) concentration is decreased in explanted sutures. Certainly the durability data that has characterized Prolene’s use in the human body for more than 50 years does not support DLTDP insufficiency. Neither does Burkley’s dog study. Simply put, there is no proof that Prolene degrades and/or oxidizes in the human body; given these data and common sense, DLTDP and Santonox R are certainly performing their prescribed duty as formulation ingredients, and therefore must be present and in sufficient quantities. One has only to review the excellent physical property data; i.e. tensile strength, elongation, modulus and toughness to confirm the long term efficacy of the Prolene stabilizer additives, DLTDP and Santonox R.

- Furthermore, plaintiff experts have provided analytical data proving DLTDP and Santonox R are extracted from Prolene by Formalin. Burkley's pristine sample was never in contact with Formalin, and thus DLTDP and Santonox R could not be removed by formalin solvation. Furthermore, Burkley's explanted sutures contained fatty materials and proteins as shown by FTIR spectra, all of whose presence minimizes the concentration of DLTDP and, thus, minimize its spectral presence. Spectral absorptions vary depending on a molecule's environment and the method of analysis, i.e. transmission microscopy, reflectance microscopy, and ATR spectroscopy.[140,141]

- Proteins are present in the spectra of explanted sutures. I call attention to Figures 10-11 and absorption frequencies in the 1600 cm^{-1} range as well as the 3300-3400 cm^{-1} region. Both are indicative of proteins. Consider the Table I statement (ETH.MESH 12831393) "the broad nature of this band (3409 cm^{-1}), along with its position suggests a primary amine…" Proteins possess primary amine functionality and thus further confirmation for protein presence.

- There is no indication of oxidation. Had there been oxidation, the spectra of Figure 11 would have shown sharp and strong absorption frequencies in the 1750-1700 cm^{-1} region and no absorptions in the 3300-3400 cm^{-1} region, and there is no 1750-1700 cm^{-1} and there is absorption in the 3300-3400 cm^{-1} region.

- I have examined documents possessing no Bates stamp but numbered 76-84 and 89-100. These are data sheets holding dates, magnifications, KV, Modes, and brief explanations of explant conditions. These data are accompanied by SEM photomicrographs numbered 2348-2436 and 86TMO 045,038,007, 87TFE002,86D050,86D077/66TM044, and numerous more 86- and 87-SEM photomicrographs with magnifications as high as 5000X. While the photomicrographs speak for themselves there is no accompanying data describing their history of origin, the fixation process, the length of time in fixation, nor any other data from which meaningful scientific conclusions can be made.

Questionable Pathological Opinions

Some plaintiff's experts have incorrectly opined as to the formation of degraded 'bark' surrounding Prolene fibers. They cite this appearance as evidence of Prolene degradation. However, they incorrectly identify this layer as I will show later in this report. I have consistently proved by LM, SEM and FTIR spectroscopy that adsorbed proteins surrounds Prolene fibers and must be considered when explant analyses of any type are being considered or conducted. For instance, some plaintiff's experts misrepresent the coloration of histology slides during the Hematoxylin & Eosin (H&E) staining process. On the one hand they say that polypropylene will not stain but on the other, state that coloration observed is attributed to staining of degraded polypropylene. It is clear they do not understand the chemistry of dyeing, which

controls the process from beginning to end, nor the chemistry of fixation. They further confuse the issue with polarization light experiments where they correctly state that both polypropylene and proteins are birefringent and thus polarize light; however, they follow these statements with attempts to identify polypropylene apart from proteins with polarized light photomicrographs.

It is basic, fundamental chemistry, and certainly basic polymer chemistry, that proteins are polymers, and formaldehyde in the presence of proteins (flesh) forms a crosslinked formaldehyde-protein polymer, i.e. the end product of the traditional "fixation" process. Polypropylene, because of its chemical structure, on the other hand, is not affected by nor reacts with formaldehyde but is surrounded by adsorbed, and consequently adhered, proteins that are "fixed" when immersed in formaldehyde. This layer of adsorbed and fixed proteins must be considered when studying or examining "fixed" polypropylene explants. However, some plaintiffs' pathologists have not, to date, recognized the "fixed" proteins produced by their immersion in Formalin by the explanting surgeon and then the histological, or slide making, process.

It is likewise well known, basic chemistry, that H & E, or Hematoxylin and Eosin stains are standard stains for routine tissue evaluations. The staining process is of a chemical reaction origin. Colors are produced when, and only when, specific acid and/or base chemical reactions occur. If a chemical reaction does not occur with H & E dyes, no color beyond that of the base dye is produced by the H&E stains. Moreover, if no chemical reaction occurs, the unbound residual stain is removed or washed away in the slide preparation process and leaves no residual stain color. Consider, for example, the following chemical reactions required for H & E stains to generate color when histological slides are processed; as illustrated in Figure 18 below.

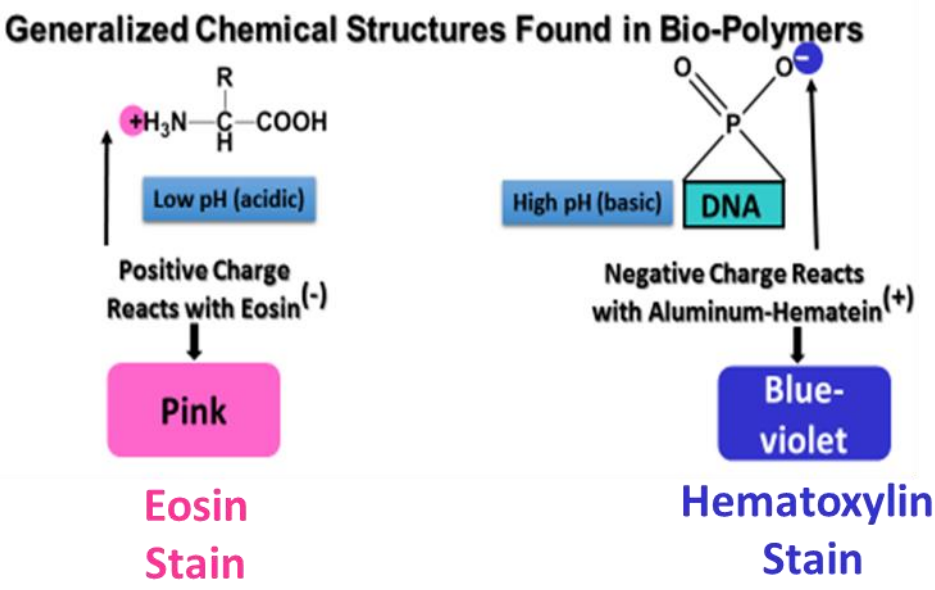


Figure 18. Chemical reactions required for histological staining by H & E dyes

By way of explanation, Hematoxylin combined with an aluminum "mordant" produces a metallic complex or "lake" holding a strong positive (+) charge. The + charged "lake" binds selectively to the negative charged (-) groups of DNA-phosphoric acid complexes.

Thus, the H & E stain turns to a dark-blue or violet color when chemically bound to substances such as DNA/RNA. These nucleic acid building blocks form salts with basic dyes, and therefore, dyes like Hematoxylin will chemically bind or react with them and stain them VIOLET.

Eosin, on the other hand, is a negatively (-) charged anionic dye (acid salt) and will react only with and bond to a positively (+) charged group. Consequently, at a pH below 6, proteins manifest a positive charge and bind with the negative charged Eosin.[142] Eosin is a red or pink stain, and consequently, Eosin binds to amino acids/proteins and stains them PINK.

In summary, while proteins (flesh) chemically react with H & E stains polypropylene does not, and cannot, due to its chemical composition. Polypropylene has no charged sites or pH, thus it has neither acidic nor basic characteristics. Simply put, the chemistry of polypropylene does not allow it to react with H & E stains and thus polypropylene is NOT stained by H&E dyes as noted in Figure 19.

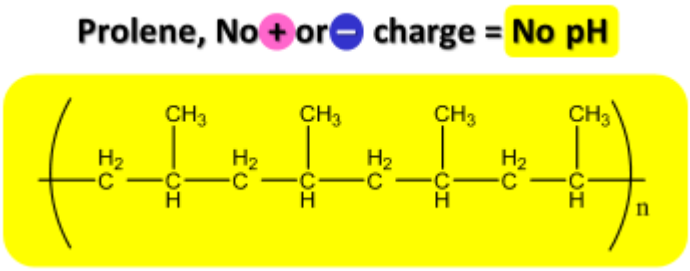


Figure 19. Prolene (polypropylene) chemical structure

However, some plaintiffs' pathologists have consistently ignored the chemistry of staining including trichrome and other stains. Rather than assign color development based on the aforementioned scientific principles, and as stated, well known chemistry, plaintiff's pathologist mis-assign color development, and thus assign substrate identification on porosity and nanostructure. They give no consideration to well know and established chemical principles of staining via chemical bonding of stains to substrates in order to achieve color.

Proof that Prolene fibers do not stain is provided in the expert report of Dr. Steven MacLean of Exponent Laboratories[143] which I rely upon. This is the type report and information I rely on in reaching scientific conclusions in my custom and practice. In Dr. MacLean's experiments TVT mesh was placed in oxidizing environments by exposure to UV light and, in a separate experiment, by the $CoCl_2/H_2O_2$ methodology used by Dr. Scott Guelcher. Neither samples accepted the H&E dye.

Response to opinions of Dr. Vladimir Iakovlev

This section will discuss my opinions regarding those of Dr. Iakovlev after reviewing his reports in the Huskey/Edwards, Bellew, Corbet, Patient 3, Iholts, Clowe, and Patient 4 cases, and his various depositions.

The March 18, 2014 Iakovlev deposition confirmed no qualitative, nor quantitative chemical analyses were performed to determine the chemical composition of mesh or any other chemical species for which he offers opinions. For instance, he states on page 209 (March 18, 2014 deposition)[144]:

> Q: The degradation analysis you did regarding Mrs. Edwards' mesh was an analysis done with microscope, correct?
> A: "I detected. It wasn't analysis."

On pages 217 and 218 he readily admits that the Edwards' explant had protein adhered to it by the following statements:

Line 25, page 217: Iakovlev's statement, "Human tissue is mostly protein."
Lines 7 and 8, page 218 he states upon questioning,

> Q: and this human tissue contains protein, right?
> A: yes
> Q: it was exposed to the formalin with the tissue on it, correct?
> A: "it" meaning mesh, yes.

The Iakovlev report of June 4, 2014 in the NJ TVT cases (page 2) states,

> Statement: "Another example of a specific finding is polypropylene degradation. The degradation material shows changed physical properties-cracking, and chemical products are released during the degradation process."[145]
>
> Response: Iakovlev provides neither reference(s) nor reliable scientific data of any kind to support his so called degradation theory. Neither does he possess nor does he provide scientifically reliable references or data to support his contention of changed physical properties-cracking. He does not characterize nor identify any so called degradation products or "chemical products that are being released during the degradation process." Consider the statements made and the lack of data supporting same; i.e. the following excerpts taken from his direct examination in the matter of Amal Eghnayem v. Boston Scientific Corp.: [146]
>
> Page 85
> 11 This is the identifier of St. Michael's Hospital. It was
> 12 received in a formalin jar
> Page 86
> 17. Q. Are you familiar with the term "loss of elasticity"?
> 18 A. Yes.

19 Q. What does that mean?
20 A. It means that the materials not elastic anymore. It's not
21 stretchable.
22 Q. What can you tell from your gross evaluation of the
23 posterior mesh about the loss of elasticity?
24 A. There was no stretchability of this tissue with the mesh.
25 I couldn't stretch it

Or

Page 87
1 I -- it also exhibited quite a bit of resistance on
2 bending. It was stiff as a plastic.

Pages 88- 89
25 Q. What about loss of elasticity? What did your evaluation of

1 the anterior mesh tell you about that on Ms. Eghnayem?
2 A. They were not stretchable. They felt like plastic.

Iakovlev neither offers nor provides any quantitative or analytical data to support his erroneous and sweeping statements. He comments that "They felt like plastic," and indeed Prolene is a plastic and it is well known that it is a flexible and strong plastic. This was scientifically and experimentally established by Burkley's 7 year dog study. Thus, his claims are scientifically unreliable and lack credibility. Moreover, Iakovlev readily admits in an August 12, 2014 deposition that he is "…not a materials scientist" (page 123, line 10), yet he opines on matters that are clearly material science.[147] He speaks of plastics in a generic sense and apparently does not appreciate "plastic" is used to include literally thousands of polymeric products, some soft, rigid, and all "in-between" properties. Elongation, modulus, elasticity, brittleness, hardness, are quantifiable properties determined by via appropriate, and well established, testing methods. Consider, for instance, the ASTM methods for determining, hardness, brittleness, elasticity, elongation and tensile properties:

ASTM D638 Standard Test Method for Tensile Properties of Plastics, ASTM D2240 Standard Test Method for Rubber Property – Durometer Hardness, ASTM D2137 Standard Test Methods for Rubber Property - Brittleness Point of Flexible Polymers and Coated Fabrics.

It is absolutely critical that any professional taking on the responsibility of evaluating explanted mesh properties, whether biological, chemical, or mechanical, possess knowledge and understanding of the process for FORMALIN FIXATION (see pages 15-21 of this report). Formalin fixation has been known and practiced by the medical community, and particularly histologists and pathologists, since 1949. Rarely are medical explants NOT "fixed" in Formalin (an aqueous mixture of formaldehyde). And in

the matter at hand, all explants were fixed in Formalin by the surgeon at time of explanting (see Iakovlev's deposition, pages 27 lines 15-20 and 28, lines 6-7.)[148,149]

When questioned about the technique for measuring stiffness, Iakovlev admits it was performed by palpation. However, Iakovlev gave essentially no consideration to the phenomenon of tissue "fixation" in formaldehyde and its effect on tissue stiffness and other properties. The "fixation" process begins in the operating room with the surgeon placing explanted tissue immediately upon extraction into a Formalin solution. The ensuing chemical reactions, defined as "fixation," fulfill their purpose by transforming explanted tissue (proteins) into a hard, stiff, polymeric composition of formaldehyde and proteins.[150] Formaldehyde hardens proteins and makes them water resistant.[151] The hard, brittle crosslinked formaldehyde polymer forms and in doing so, "fixes" or transforms the explanted tissue into a rigid mass, as is its primary purpose. Explanted tissue must be "fixed" or transformed into a hard, stiff or otherwise brittle state for tissue slicing by a pathologist. If no "fixation" occurred, explanted tissue would simply be too soft to affect smooth tissue cuts required for histological evaluations. Thus, explant "fixation" produces a shell, or "bark" as it is called by Iakovlev, surrounding, and otherwise encasing, the fiber. There is no dispute that explants treated and fixed with Formalin may be perceived as stiff via palpation (page 32, lines 9-10).[152] However, neither is there dispute by those knowledgeable in the field that fixation (protein crosslinking), accompanied by mesh shrinkage after explanting, contributes to the "feel" of stiffness. This thesis is further confirmed via Iakovlev who states; "The stain is showing if there is calcium in the tissue, so pretty much all fragile, brittle tissues in human body contain calcium, that's why they're brittle. I saw the bark is cracking, so my question is, is it because of calcium inclusion, and that's why I did calcium staining. And it wasn't – didn't contain any calcium."[153] (page 34, lines 4-8)." It is instructive in this matter that the "bark" did not contain calcium, yet the tissue was stiff. This circumstance is consistent with formation of a hard, brittle substance, i.e. the crosslinked "fixation" product (page 52, lines 24-25) which, given his testimony, the deponent clearly does not understand or chooses to ignore (page 54, lines 13-16; page 57, lines 1-6).[154] To further add credence to the "fixation concept" and its effects on flesh, Lester[155] in the Manual of Surgical Pathology writes:

"Ideally fixation serves to:

- Harden tissue to allow thin sectioning
- Preserve tissue
- Stabilize tissue components
- Enhance avidity for dyes
- Alter protein structure which may be crosslinked
- Shrinkage of tissue: Most fixatives cause shrinkage of the tissue. If exact measurements are important they should be taken prior to fixation.
- Over fixation may result in hard brittle tissue in some fixatives."

Tissue hardening, crosslinking, tissue shrinking, over fixation, and distortion are all by-products of the "fixation" process; a process which Iakovlev totally dismissed in his analysis.

Finally, my opinion of the deponent's lack of awareness and/or understanding – or failure to consider -- of this critical formalin "fixation" process and its effects is conclusively confirmed by his several deposition statements that follow:

See deposition, page 221 lines 9-25 and page 222 lines1-4 wherein he admits he is unsure what the term "protein polymer means."[156]

Page 221-222:

Q. You know that when formaldehyde bonds with protein polymers a new polymer is formed?

A. Please repeat the question?

Q. Sure.

Do you know that when formaldehyde bonds with protein polymers a new polymer is formed?

A. Protein polymer; I'm not sure what you mean.

Q. Okay, is that a field outside of your expertise?

A. I'm not sure if such thing exists, a protein polymer. Maybe since any sort of setting, if you accept—polymer is something with relatively homogeneous simple molecule which is being linked into continuous chains. Proteins are completely different structures. So I don't think this is a correct term."

It is basic, fundamental chemistry, and certainly basic polymer chemistry, that proteins are polymers, polypropylene is a polymer, and formaldehyde in the presence of proteins (flesh) forms a formaldehyde-protein polymer, i.e. the end product of the "fixation" process.

See also the following quotes from Dr. Iakovlev's report for the NJ-TVT cases:

"Several observational and experimental studies showed that polypropylene used in the mesh degrades while exposed to the body environment."[157,158]

"Microscopic examination of the explanted meshes shows a layer of homogeneous material at the surface of mesh filaments (Figure 18b). The layer stains light-purple by the hematoxylin dye, while the central core of the filament does not absorb the dye."[159,160]

"Also, the material tends to adhere to the glass slide and tissue, while the central core peels off the glass slide. To investigate the nature of this material it was

examined under polarized light as well as tissue was stained using immunostains for immunoglobulin and myeloperoxidase."[161,162]

Response:

The homogeneous material at the mesh surface is undeniably crosslinked formaldehyde-protein polymer to which Iakovlev gives absolutely no consideration, nor has he performed any chemical analysis to rule it out. Moreover, he readily admits that "the layer stains light purple by the Hematoxylin dye, confirming its proteinaceous nature. He further states, that the "central core of the filament does not absorb dye," and that is to be expected given the central core is Prolene. Prolene does not accept H & E dyes. Finally, his statement "Also, the material tends to adhere to the glass slide and tissue, while the central core peels off the glass slide," is certainly to be expected. The reason; Prolene has no structural features allowing it to adhere to glass, while proteins are known for their tenacious adhesion characteristics. The "fixation" chemical reaction and the products derived therefrom was established in 1948 and published in scientific literature in 1949.[163]

Thus, if proteins are attached to the surface of Prolene (and they are), and formaldehyde or Formalin solution is present, it is undeniable that crosslinked protein-formaldehyde polymers form. Given Formalin is a standard "fixative" in operating rooms worldwide, the remaining ingredient must be proteins for the "fixative" process to proceed. Thus, the stage is set with ideal reaction conditions for formation of the crosslinked protein-formaldehyde reaction to occur, and it does. The crosslinked protein-formaldehyde polymer readily accepts stain, while Prolene, a hydrophobic, charge neutral, hydrocarbon polymer, does not. Proteins, on the other hand, are excellent bonding agents to hydrophobic materials such as Prolene according to Schmidt who states "Consequently, enhanced protein adsorption and conformational change are observed on hydrophobic surfaces."[164] This statement provides a sound and logical explanation for Iakovlev's observation that "Also, the material tends to adhere to the glass slide and tissue, while the central core (Prolene-being hydrophobic and non-polar) peels off the glass slide." Thus, the homogeneous material at the mesh surface which Iakovlev calls "bark" is not Prolene nor-degraded Prolene; rather it is the crosslinked formaldehyde-protein shell surrounding Prolene fibers. Furthermore, Iakovlev provides absolutely no chemical analysis of any kind to confirm the chemical composition of his so-called "bark." He is obviously unaware that formaldehyde reacts with amines and proteins and in doing so forms a strong adhesive bond to the substrate it surrounds (Prolene); proteins are known for their tenacious adhesion.[165] This is such an important concept that the following deserves being quoted;

- "A good perspective for adoption by the novice approaching this field (*Theory and molecular mechanisms of protein adsorption*) is that all proteins adsorb to all surfaces. It is rarely a problem how to achieve the adsorption of a protein, but rather how to prevent it. Consequently, protein adsorption is the central event in the biofouling of surfaces."
- "Surface properties have an enormous effect on the rate, the extent, and the mechanism of adsorption. Perhaps the broadest, most widely accepted

generalization regarding surface properties concerns hydrophobicity and holds that the more hydrophobic the surface the greater the extent of adsorption."

- "Also proteins are large molecular entities which usually contain many charged groups, some negative and some positive."[166]

It is worth reiterating that the "central core" in Iakovlev's work is Prolene; Prolene is neither acidic nor basic, it is neutral in charge, and therefore it does not, and cannot by its chemical structure, react with dyes and become colored. However, the porous outer layer or "bark," as it is called by Iakovlev, is a crosslinked formaldehyde-protein polymer, a result of the formaldehyde "fixation" process of adsorbed protein which possesses (+) and (-) charged chemical structures that readily react with H&E dyes. Iakovlev states the observed outer layer is "synthetic" which is consistent with crosslinked formaldehyde-protein polymer embedded in, and reacted with, preserved flesh.

The Iakovlev report describing experimental (ibid, page 9, last paragraph)[167] comparisons of polypropylene samples supports the tenet of Prolene not degrading *in vivo*; for instance, consider the following:

1. Mesh with 9 year *in vivo* exposure
2. Mesh with 1-year *in vivo* exposure
3. Mesh unused, new-no *in vivo* exposure

Explanted mesh samples 1 and 2 were again subjected to formalin fixation, after which they were paraffin embedded and underwent staining procedures.

RESULTS

1. 9 yr. *in vivo* exposure------detectible thicker outer layer absorbing hematoxylin dye (4-5 micron thick).
2. 1 yr. *in vivo* exposure-------thin outer layer absorbing stain-(1-2 micron thick)
3. Mesh unused, new-------no stainable layer.

Figures 18, 19a & b; 20 a&b and 21

Iakovlev makes the following statement, "The only differences I have detected so far is the thickness, where the bark with 1-year of *in-vivo is* detectably thinner than the bark of specimens of >3 years *in-vivo* exposure." (Pages 9-10). In addition, Iakovlev compares *in vivo* exposure to "degraded layer thickness" on page 10 of his Patient 3 report, stating that there is a "strong association between the bark thickness and the mesh in-vivo exposure." [168]

These data support the following explanation:

1. First, if pristine Prolene is treated with formaldehyde, no proteins are present to allow for a deposit of any kind to form on the Prolene fiber**.** Prolene alone will not react with formaldehyde to form an outer shell. Proteins must be present for formalin to react, and proteins are not present on pristine Prolene.

2. The longer implantation time, the thicker the bio-layer or protein deposition on Prolene. With extended time, there is access to more proteinaceous material for fixation, and the fixation process continues for the duration of fixation and, in the process, will "fix" more and more bio-layers of flesh. In summary, protein thickness continues to grow over time. The longer the implantation time and/or the longer the fixation time the thicker the build-up of the crosslinked formaldehyde-protein layer around the Prolene fiber surface. Thus, the nine year explant would be expected to exhibit the thickest crosslinked formaldehyde polymer shell or armor.

3. Iakovlev did not provide chemical characterization data, such as FTIR spectroscopy, to scientifically establish or prove the material adjacent or adhered to Prolene is anything other than a crosslinked formaldehyde-protein shell. However, that the shell is proteinaceous in composition was confirmed by other plaintiff's expert, and me, using FTIR spectroscopy analysis.

4. Finally, Iakovlev has not provided or used a control specimen of degraded Prolene, or PP for that matter, and scientifically proved his statement, "outer bark of degraded polypropylene absorbing dye."(Figure 19a. 9 years in-vivo exposure, page 37).

   Consider the following:

   Iakovlev has not identified or utilized a control which is known-to-be-degraded polypropylene. This is absolutely necessary in order to establish stain reaction with and thus dyeing of so called degraded polypropylene. Therefore, his statements have no support of an experimental control, nor any data that would come therefrom. Consequently his conclusions have no merit, scientific or otherwise, or basis-in-fact and are, therefore, flawed, unreliable, and scientifically invalid**.** His thesis that Prolene, if degraded, would absorb stain, is pure supposition with absolutely no supporting scientific data, and is inconsistent with known chemical reactions of H & E stains.

   Iakovlev has used flawed methodology in developing his opinions which have no basis in fact.

5. Iakovlev's report contends the explant's outer stained layer is Prolene. Yet he has stated Prolene does accept dyes. The existence of a protein-formaldehyde polymer must be accounted for, and it is, as the stain

accepting outer, porous layer of the crosslinked formaldehyde-protein polymer shell that Iakovlev incorrectly identifies as degraded polypropylene or "bark." I must emphasize polypropylene or Prolene does not accept dyes and therefore is not colored by dyes.

6. Although Iakovlev readily admits to "fixing" all explants in Formalin he completely ignores the chemical product formed by the fixation process, and gives no attention to determining its presence, its composition, nor its location in his various photomicrographs. He has improperly labelled and characterized it as degraded Prolene "bark."

7. The Iakovlev report states (Ibid: page 10)[169] "The surface of the "bark" was irregular and had multiple cracks, where some cracks extended through the full "bark" thickness and either stopped at the bark-core interface or turned parallel to it (Figure 27)." If this were a scientifically valid statement, and the "bark" was indeed Prolene, one would observe crack propagation through the entire mesh fiber, and fiber breakage or rupture would be the end result. This did not occur, there was no crack propagation, and there was no Prolene degradation of the *in vivo* explants.

8. The Iakovlev report states, "Mesh degradation alters polypropylene properties." However, the report is absolutely devoid of any scientific data confirming which, if any, Prolene properties were compromised, or altered. As a matter of fact, Burkley's 7-year dog study scientifically and unequivocally established and affirmed Prolene's physical property improvement during 7 years of implantation. Iakovlev makes no mention of the Burkley 7 year dog study.

   The Iakovlev report states, "The degraded layer has cracks showing its loss of elasticity and hardening. As a result, it introduces changes to polypropylene mechanical properties and therefore contributes to mesh deformation and hardening." Once again**,** the Iakovlev report is devoid of any scientific data to support these assertions. He has totally dismissed the teachings of Dr. Susan Lester, a pathologist, in the Manual of Surgical Pathology wherein it is stated under the topic of "Shrinkage of Tissue: Most fixatives cause shrinkage of the tissue."[170] This effect is due to molecular contraction as the formaldehyde and proteins react and lose a molecule of water in the process. The loss of water draws the two reactants closer together and thus "contraction" as a result of fixation. "If exact measurements are important they should be taken prior to fixation."[171] Moreover, he has dismissed the work of Burkley who showed physical property enhancements of Prolene after 7 years *in vivo* implantation in dogs.[172] He has further dismissed the well-known polymer forming crosslinking reaction of formaldehyde reacted with proteins produces a hard, brittle outer shell surrounding Prolene fiber(s).

9. The Iakovlev report states (page 10) "The outer bark showed remaining blue granules in the inner parts of the bark, which further proves that the outer layer indeed originates from the filament material (Figure 24)."[173,174] It is not surprising that some blue could be seen under microscopic examination in the inner-closest layer to the Prolene fiber. Solvent softening by xylene, [175,176,177] handling, molecular contraction, manipulation and cutting of the "fixed fibers" in preparation for testing, slicing, and any other physical function could readily cause some degree of cohesive bond rupture seemingly opening up and/or softening the Prolene surface layer and appearing as an artifact. Moreover, the angle of observation can and does alter what one "sees" in the microscope objective. Finally, Iakovlev cannot distinguish between blue spots derived from H&E stains and Ethicon pigments; both are blue.

   In fact, Iakovlev testified (March 18, 2014 deposition; page 232) to the following:

   > Q: What is that? Are those spaces in connective tissue?
   >
   > A: Yes. This is just a separation during the processing. I would have to look in the microscope. But sometimes tissue gets little bit of retraction space when it's being processed, it retracts, so there's artificial empty space."
   >
   > Q: Is that what pathologist talk about when they reference artifacts from the processing?
   >
   > A: Yes, retraction, tissue retraction is an artifact.

   In this same deposition Iakovlev was questioned as to why "bark" takes up stain (page 302) to which he answered, "Why barks take the stain? It's porosity. The porous cracks, they just trap histological stains specifically." Iakovlev is likening the staining process to a physical phenomenon of being trapped in voids, rather than the well-recognized acid-base chemistry for color generation.[178] This Iakovlev response is proof-positive he lacks understanding of the chemical process of staining and the required acid-base reactions. Moreover, it is well established that crosslinked formaldehyde-proteins are hard, brittle and porous and according to Iakovlev's theory they too would absorb H&E stains. Indeed they do absorb H&E stains but not because they are porous; but because they possess and hold (-) and (+) charged chemical species.

10. Finally, the very "fine, smooth, line of demarcation" between the formaldehyde-protein polymer and PP fibers (See Fig. 24a, 24b, and 24c), is indicative of two dissimilar materials.[179] H & E stains nuclei PURPLE and that is exactly what Iakovlev has shown in Figure 24c. The segment of slide he states is degraded bark is dyed PURPLE, and consequently, by

his own admission polypropylene does not stain, and therefore cannot be polypropylene. However, even in the face of his own writings, he speaks of the PURPLE layer as, "The degraded bark shows optical properties of polypropylene, however is brittle and readily separates from the non-degraded core." He has stated on numerous occasions PP cannot be dyed and this is a contradiction in fact.

Furthermore, Iakovlev fails to speak completely to Figure 24d or 24e of his Patient 3 report (page 66) which is enlightening and explanative of Figures 24a, b, and c.[180] For instance, this figure (24 d, e) provides microscopy data in regular and polarized light. He states the "degraded bark shows optical properties of polypropylene, however, it is brittle and readily separates from the non-degraded (polypropylene) core." What he fails to say is that collagen proteins are birefringent and as such possess two refractive indices, and thereby they (collagen) respond to polarized light.[181] Iakovlev confirms this on page 66 of the Patient 3 report with the statement "Note the dark collagen in the lower right."[182] In this instance, the protein coating is crosslinked with Formalin. Finally, close observation of Fig. 24d (in regular light) confirms the separated and broken section between polypropylene and the remaining tissue (to the right) as showing blue-violet and well as red stain, respectively; thus confirming both are of flesh origin (not polypropylene) and are the colors one would expect from H&E staining. When this identical portion of the stained slide is subjected to polarized light, it responds to polarized light, confirming once again that proteins show the same optical properties when viewed with polarized light as polypropylene. Therefore, one cannot use polarized light to chemically distinguish between polypropylene and proteins.

Further evidence that Iakovlev's conclusions are scientifically invalid and incorrect is found in his Trichrome Stain data (see page 116, July 7, 2014 Rule 26 Expert Report of Vladimir Iakovlev).[183] Figure DB-15 of this report is titled "Appearance of the degradation bark in trichrome stain." It is instructive that:

- He assigns the red areas of the slide as "Red dye within smaller micropores of degraded polypropylene." However, the 2010 Lamar Jones Technical article in CONNECTION clearly states collagen stains blue or green depending on the collagen stain utilized (page 83) and the final staining results are: Cytoplasm, fibrin, muscle stains red, and Collagen - light green (page 84).[184] Note that Jones' assignments deal with tissue (reactions. However, Iakovlev erroneously assigns the staining colors of Fig. DB15, not as tissue, but as polypropylene degradation:

  -Red as dye within smaller micropores of degraded polypropylene

-Blue as granules retained in degradation bark, and

-Green as dye within larger micropores of degraded polypropylene

It is clear Iakovlev does not rely on the chemical reactions of tissue with stains, but on some sort of undefined physical porosity, in stark contradiction to printed, technical manuscripts describing the staining process otherwise.

Iakovlev's opinions and statements are based on flawed methodology. They are in direct contradiction to well established scientific principles of tissue staining. Consider the Jones Technical Bulletin titled "Mastering the Trichrome Stain."[185] Therein it is stated in the introduction section, "At the onset it must be made clear that the methods control how ionized acid dyes react with ionized basic tissues. This is the fundamental principle on which they depend and the explanation is only about how that fundamental reaction can be manipulated."[186] Following this is a statement of purpose, "The purpose of the trichrome stain is primarily to demonstrate collagen and muscle in normal tissue or to differentiate collagen and muscle in tumors."

The Technical Bulletin further notes that "collagen appears white in the fresh sate, is birefringent when polarized with light" as is polypropylene.[187]

The overall discussion of mesh shrinkage in the Iakovlev report is surprisingly devoid of Dr. Lester's[188] reference regarding formalin induced tissue shrinkage and its effects on properties. I am further confused by the Iakovlev deposition description of how Prolene degradation was determined. For instance, consider pages 295 (line 24-25) and page 296 (lines 1-18) of the Iakovlev deposition. In essence, Iakovlev states proteins take up stain and that is called protein expression; he further states Prolene does not stain, given it is hydrophobic. Yet, he uses these data to conclude Prolene degradation and I see no correlation between the data he cites and Prolene degradation.[189] His opinions are contradictory and are based on flawed methodology. Simply put, human flesh made principally of proteins react with dyes and produce color, while Prolene, a hydrocarbon polymer, is amphoteric, hydrophobic, does not possess positive or negative charges and consequently does not react with dyes and therefore does not produce color. The Iakovlev report states staining is used to ascertain the amount that stain soaks up in a material and describes this as "measuring protein expression." He states stain intensity measures the amount of expression of a protein. There is no explanation of how measuring protein expression can or will determine Prolene degradation. In my view it absolutely cannot, and the Iakovlev report does not contain scientific data to support the contention that Prolene degrades in the human body. Iakovlev presents additional opinions on pages 302-303 regarding alleged degradation. Iakovlev readily agrees that: "cracked material in the surface, it can be either polypropylene crack or protein."[190] He has not isolated nor analyzed the so called "bark" yet alleges he can "see that the bark is synthetic, polarized acts as a polypropylene optically, it is a polypropylene. This is the

type chemical analysis I do under microscope. I analyze optical properties of the material." One cannot determine a material's chemical composition by viewing its optical properties with a light microscope.

Moreover, I have consistently shown unequivocally, via FTIR spectroscopy analysis, the outer layer or deposit on explanted Prolene is protein, and by Iakovlev's admission, proteins will absorb dye, while Prolene will not.[191]

It is important to pay close attention to the Iakovlev statement "the layer of degraded bark is seen in all polypropylene mesh explants I examine, irrespective of their exposure to vaginal environment or acute inflammation." This statement is further confirmation of the widespread and pervasive use of formaldehyde-protein crosslinked fixation in surgery, and the well-established fact that proteins instantly and efficiently adsorb upon Prolene's surface after its implantation.[192] Moreover, it clearly establishes the presence of the formaldehyde-protein composite polymer on explants. However, Iakovlev's opinions give no attention to, or admission of, the flesh-protein-formaldehyde polymer formed during the fixation process. He completely ignores its presence. Consequently, among Iakovlev's opinions are, the formaldehyde-protein polymer does not exist; and this is patently incorrect. We know his opinions are incorrect given the fact all explants delivered to and evaluated by Iakovlev were fixed in Formalin, and the 1949 Fox article on formaldehyde-fixation is very well-known. [193] These facts cannot be disputed. Thus, factors all explants have in common are, all are fixed in formaldehyde, all contain flesh, all form a formaldehyde-protein polymer or shell around PP fiber(s), and all are subjected to histologic tissue processing. This sequence of events and polymer formation, is not recognized, or is ignored, by Iakovlev. Thus he employs a flawed methodology for arriving at his opinions.

The Iakovlev report of July 7, 2014 (page 3) states, "Another example of a specific finding is polypropylene degradation. The degradation material shows changed physical properties-cracking, and chemical products are released during the degradation process."[194,195] However, no reference(s), nor scientific data exists for these erroneous and sweeping statements. The claims lack credibility, are scientifically unfounded, and consequently are unreliable. He has not provided data for any physical property change, no data to confirm which, if any chemical products, are released during the so called "degradation process," and no data to confirm chemical degradation of Prolene.

Iakovlev once again states (page 3) "Most specimens come as formalin fixed tissue …" thus all samples used in Iakovlev's work were fixed in formaldehyde.[196,197]

Iakovlev states (page 5) "degradation bark measured by eyepiece micrometer in filament cross sections closest to a perfect circle." However, he has no proof that his so called "bark" is degradation of any type.[198,199]

Section 1.3 (page 9) speaks to the issue of mesh hardening via gross examination, in part.[200,201] Yet there is no mention that "formaldehyde-protein crosslinking fixation" of the explants to which he referred, significantly influences mesh hardness. Neither does

he speak to the issue of fixation, the chemical reactions involved, molecular contraction, nor the hard, brittle shell formed as a fixation process product. Thus, any opinions rendered without due consideration of this well-known chemistry are without proper scientific consideration **or** support.

The statement "Several observational and experimental studies showed that polypropylene used in the mesh degrades while exposed to the body environment" (page 11) is without references or any corroborating scientific proof.[202,203]

The statement "The granules lost the color at the more degraded outer layers (Figure 25a, b, and c)" deserves a response:[204,205] No technical or scientific evidence is provided to support the statement "granules lost color."

> Response: Iakovlev states the bark originates from "polypropylene itself." Close examination of 25a, b, and c confirm the angle of observation and the fiber depth of observation must be considered as well as the tenacious adhesion of the protein-formaldehyde fixation product. Moreover, the colorant, CPC or copper phthalocyanine blue is supplied in powder form and dispersed during the extrusion process.[206,207] Thus, attempts to determine degradation based on visual observation of colored powder dispersion is highly suspect and without scientific merit.

The statement "Further proof that the outer layer is a synthetic material was obtained from immunostaining for myeloperoxidase….." (Page 12 Iakovlev report).[208,209]

> Response: The outer layer, as described by Iakovlev, has been confirmed by plaintiff's expert and me to be proteins.[210,211] Iakovlev's statement continues with "Since the bark is brittle (cracking), a calcified material needs to be ruled out. Nearly all hard brittle structures in the human body are hard due to calcium deposition." However, Iakovlev is discounting the hard and brittle crosslinked protein formaldehyde polymer formed during fixation. The fixation product is well known to be hard and brittle and does not require the presence of calcium to be characterized as such.

Iakovlev's section 1.4.2.1. (Page 12) titled "Ruling out manufacturing coating and formalin fixation artifacts" is totally without merit.[212,213] Consider the statement, "Samples of unused, new trans-obturator tapes of Ethicon and another manufacturer were subjected to the same formalin fixation, chemical processing, paraffin embedding and staining procedures as diagnostic specimens. The meshes were placed in formalin and samples of mesh were taken at 1 week, 1 month and 4 months. After 4 months of formalin fixation the new mesh showed no stainable layer (Figure 29a, b).

> Response: Of course not, none would be expected given there was no flesh present, and since there was no flesh, no proteins were included in the test. The test did, however, prove that polypropylene does not react with nor accept histological stains. Note the last sentence where Iakovlev speaks of tissue

processing, and claims that his test rules out processing as a cause of the "bark". The experiment and conclusions are without merit given no tissue was present for formalin fixation and there was no opportunity for artifact formation.

Section 1.4.2.2 speaks to the issue of electrocautery effect on bark.[214,215] The surgeon removing the tissue used temperatures exceeding 200°C degrees to cauterize flesh in order to reduce bleeding. However, proteins are tenaciously bonded to Prolene *in vivo* and cauterization exposes both Prolene and proteins to high temperatures instantaneously. Accordingly, Prolene will melt and flow freely at this temperature (Prolene melting point is app. 162°C). The result would be a composite like structure including both materials; Prolene and the formaldehyde-protein composite. No confirming analytical data such as FTIR spectroscopy was reported as having been performed for these sites, and one absolutely cannot determine chemical composition based on light microscopy. Moreover, the statement "The bark also mixed together with the non-degraded core during melting forming common pools indicating that the core and the bark are of the same original material" is without any scientific foundation.[216,217] It is not a requirement for one to have "the same original materials" to form a "common pool" of melt. The melting process transforms Prolene into a liquid which will encompass adjacent or joining materials and in so doing, form a single mass, both of which may be melted. When Prolene is transformed into a hot flowable liquid by melting, the extent or direction of flow cannot be controlled.

The Iakovlev, Section 1.4.2.3 Relationship between the bark thickness and *in vivo* exposure, makes the statement, "The correlation coefficient was showing a strong association between the bark thickness and the mesh *in vivo* exposure indication its formation while *in vivo*."[218,219]

Response: It must be remembered that all tissue examined by Dr. Iakovlev was fixed in formaldehyde by others prior to Iakovlev's sample receipt and analysis, and consequently formation of the formaldehyde-protein polymer shell around PP fibers occurred prior to Iakovlev taking possession of the explants. Thus, Dr. Iakovlev once again discounted the known chemical reaction of formaldehyde and protein with this and other statements.

Section 1.4.3 Transmission electron microscopy (TEM) in part confirms my work and my conclusions.[220,221] That is, Iakovlev's "bark" is distinctly different from Prolene, it is more porous than Prolene, and it measures in the range of 4 microns. My work has likewise shown the crosslinked polymer of formaldehyde-proteins to be irregular, with multiple cracks, some cracks extending through the full formaldehyde-protein polymer, and either stopped at the Prolene surface or turning parallel to it.

An important, and telling, observation by Iakovlev is that the cracked protein-formaldehyde polymer shell (called "bark" by Iakovlev) did not extend into or through the PP fiber. Consequently, there was no crack propagation into Prolene, and no loss of Prolene mechanical properties would have occurred. Had the so called "bark" been Prolene, the crack would have propagated through the entire fiber resulting in fiber

cleavage. Crack propagation is a well-established concept.[222] The fact the cracking material did not propagate into and through Prolene confirms it is not Prolene.

Dr. Iakovlev's opinion of, the "degradation and cracking of PP" with the findings of cells wedged in the cracks, lacks merit. One must consider the explants when removed, placed in formalin, handled by the surgeon, then handled by those who removed them in Dr. Iakovlev's laboratory, and while preparing them for microscopy studies, particularly during the microtoming process. Given these wet materials are flexible, with a hard, brittle polymeric shell surrounding the fiber, tissue or cells can physically find their way to the cracked protein-formaldehyde polymeric shell during any one of these slide preparation maneuvers. Moreover, flaking of the protein-formaldehyde polymer itself into the "cracked" areas could readily occur. In any event, there are multiple opportunities for the "cracked" areas to be partially filled by fragmented polymeric materials.

Iakovlev makes the statement "The surface defects were filled by extracellular tissue matrix and there were sites of collagen anchoring to the surface (Figure 37)." This explains the adherence of the so-called "bark" to the tissue" yet is omitting one very important concept; i.e. Iakovlev's "degraded bark" is crosslinked formaldehyde-protein fixed tissue, they are one-in-the-same, and formation of strong adhesive and cohesive bonds are expected and known to occur.[223]

The statement, "Mesh degradation alters polypropylene properties" is completely without merit or supporting scientific data, as is Iakovlev's following statement "The degraded layer has cracks showing its loss of elasticity and hardening."[224,225] Iakovlev follows these two erroneous statements with "As a result, it introduces changes to polypropylene mechanical properties and therefore contributes to mesh deformation and hardening," for which he possesses absolutely no supporting evidence. To the contrary, Dan Burkley's 7 year dog study proved unequivocally physical properties of implanted Prolene improves during implantation, not diminishes. After explanting and testing sutures it was experimentally confirmed that implantation provided significant mechanical property improvements such as toughness and elasticity, with no loss in molecular weight.[226] Mesh deformation/molecular contracture is well known to be a result of the formaldehyde fixation process, and is accompanied by hardening.[227] Burkley's suture explants were not "fixed" in formalin, and thus the crosslinked formaldehyde-protein polymer formed during the fixation process did not and could not form.

Iakovlev's section "Polypropylene Degradation," page 94 of the Iakovlev July 7, 2014 report states:[228]

- "Polypropylene, as shown, degrades in the human body forming a layer of degraded material resembling a tree bark. The bark retains the blue granules and optical properties of original material, however, it shows porosity/cracks and brittleness, which is not seen in the non-degraded polypropylene. This indicates

> that degraded polypropylene forms a continuous hardened tube-like sheath with altered physical characteristics."

The prior statement is indicative of all Iakovlev's explant examinations. His statements continue to be without consideration of the well-known and critical, to this issue, chemical reactions of "tissue fixation." All human proteinaceous material will react with formaldehyde (formalin) and the result is forming of a crosslinked polymeric structure.[229] In the present instance, human tissue completely encapsulates explanted Prolene fibers, and consequently the crosslinked formaldehyde-protein polymer formed and surrounded the Prolene fibers. This polymerization process produces a hard, brittle, and insoluble shell surrounding explanted Prolene fibers. It is this reaction that typifies "flesh fixation," and that is its purpose. While the medical community has utilized this process for more than 50 years, its fundamental chemistry is apparently overlooked, but is central to the understanding of the issue in question. Flesh, bacteria, inflammatory cells, all possess proteins and consequently Prolene's surface is surrounded by proteinaceous materials, all of which possess strong adhesion to Prolene. Thus, it is not unexpected that drying the protein layer, and physical manipulation for its removal, would result in some artifact formation outside the body. This phenomenon has been confirmed and reported.[230]

Dr. Iakovlev has ignored the chemistry of fixation. He has ignored its resulting dramatic transformation of flesh properties. Dr. Iakovlev has mis-assigned formation of the hard, brittle protein-formaldehyde polymer as degraded Prolene. He readily admits Prolene does not receive dye but contends the "bark" or degraded Prolene as he calls it, does take dye and is stained. These are contradictory statements. He makes such assertion without any scientific supporting data. Furthermore, he has not, according to his report, produced degraded Prolene and determined its dye characteristics. Therefore, he has no way to know how degraded Prolene "looks" or "takes dye" any differently than pristine Prolene. Simply put, his methodology is flawed as he has no "scientific control" from which to draw conclusions. Consequently, his assertions are totally subjective and disregards the 60+ year old chemistry of the fixation process, and its effects on explanted Prolene and Prolene examinations.

Iakovlev continues with the following, "Cracking indicates shrinking forces within the bark. Degradation products are released in the tissue and play a role in the continuous inflammatory reaction and additional complications." It is well known within the medical community, and particularly among pathologists, that the "flesh fixation process" causes tissue shrinkage. This well recognized and publicized fact is ignored in the Iakovlev report.[231] It is interesting that Iakovlev, a pathologist, is apparently unaware of this process and its effects.

Moreover, Iakovlev's statement "degradation products are released in the tissue…," is without any scientific data and should be disregarded. See page 302, March 18, 2014 Iakovlev deposition wherein the following question and answers were proffered:[232]

> Q: The crack can be from the body's proteins, that's one source?

A: Yes

Q: And another source for your opinion is that the cracks can be from degraded polypropylene?

A: Yes. So if you see cracked material in the surface, it can be either polypropylene crack or protein.

Q: Did you attempt to isolate this bark that you opine is in the slides and chemically analyze it?

A: No

Furthermore, in a series of questions regarding proposed degradation and the hypothesis for degradation, the following dialogue occurred (page 306)[233]

Q. There's people who analyzed whether there is alleged oxidation, and they found that there is no oxidation. You're aware of that research, correct?

A: I don't know. This is polypropylene, it's completely different, behaving differently than non-degraded polypropylene. And it doesn't form by formalin alone, it forms *in-vivo.*

The statement "it forms *in-vivo"* is sheer speculation as he has absolutely no way to know that formation of the "bark" occurs *in-vivo,* given he first receives the explants after they have been "fixed" in Formalin.

To further confirm Iakovlev's flawed attempts to establish Prolene degradation via staining and microscopic examinations, consider his trial testimony of November 6, 2014 (Amal Eghnayem vs. Boston Scientific). His testimony on page 95 reads (lines 3-5) as:[234]

A: "Chronic foreign body inflammation is mainly microphages. You can see dots. These are blue dots of the nuclei of microphages." That being said, consider his statement of page 100, lines 10-12; "And the background clear material is clear polypropylene. The blue dots within it are the blue granules which are added to color it."

Given he has no analytical data to confirm chemical composition of the "blue dots" and his identification of two very dissimilar materials as "blue dots," one macrophages and the other polypropylene, it is clear Iakovlev's opinions lack scientific standing and to say the least, are misleading, confusing, and simply wrong.

Iakovlev continues his unsupported testimony in the matter of Maria Cardenas on August 18, 2014, page 581 beginning at line 7.[235] Iakovlev testifies, "In this case, the long chains of polypropylene are broken down, and there are microcavities in it. Then the next step for me was to see if this – this layer is, in fact, polypropylene, and I examined it in polarized light. We use polarized light in pathology to identify foreign bodies." He continues on line 20 with, "In this case, polypropylene polarizes light, we can see it, and the bark which is peeling off is also bright. So this finding indicates that

the bark is, in fact, polypropylene." I have established within this report, with scientific references, that proteins are also birefringent in polarized light and consequently polarized light cannot be used to distinguish the presence of only polypropylene in the presence of proteins, as proteins are likewise birefringent and polarize light. Iakovlev continues testimony on page 583-(line23) and 584 (lines 1-3) respectively, with statements, "Then I can examine the same sections in polarized light, and polypropylene becomes bright, you can see it, both the degraded part and non-degraded part." "All foreign material is bright." A protein-formalin composite structure is a foreign body, yet Iakovlev gives absolutely no consideration to its presence.

It is scientifically invalid to make sweeping statements without supporting scientific evidence. Consider for instance, page 126 of the Nov. 6, 2014 trial testimony:[236]

> Q: (line 5-7) Doctor, can you cite to any literature that you rely upon for the appropriateness of using polarized light to evaluate potential degradation of a polymer?
>
> A: (lines 13-15) In terms of polymer, I don't know. In terms of polypropylene and histological sections, no. My publications were the first publications.

Dr. Iakovlev's statements amount to an unsupported theory that raises more questions than provides answers. Consequently, Iakovlev's writings hold no scientific merit, and by his words are scientifically unsupported. Iakovlev is completely unaware of, or chooses to ignore, the formation of the fixative crosslinked formaldehyde-protein polymer, and that proteins are polymers.[237] Iakovlev has leaped to the conclusion and mischaracterized the crosslinked protein-formaldehyde polymer shell as Prolene; a fundamental flaw in his conclusions. Iakovlev's theory that the outer dyed layer is degraded Prolene, does not account for the obvious "protein fixation" product. It also does not account for his own writings that Prolene does not accept histological dyes. It is obvious Iakovlev's "bark" is the dye accepting outer, porous layer of the crosslinked formaldehyde-protein polymer shell. It is well known, and Iakovlev agrees, proteins accept dyes while polypropylene does not. It is my belief that Dr. Iakovlev's opinions regarding degradation of Prolene in the human body are erroneous, unsupported, incomplete, and scientifically unfounded.

Iakovlev states in his July 7, 2014 report (page 4) "To understand the related pathological processes and make a correct diagnosis, pathologist need to understand the function of the devices being analyzed, their physical characteristics, surgical and other techniques introducing the objects into the body." He goes on to state, "I possess this knowledge and expertise and these routine methods were used for assessment of explanted meshes." However, when reading this same report it became very clear that he does not appreciate or understand the full implication of the "routine methods (he) used for assessment of explanted meshes."[238] Those "routine" methods involved mesh fixation and its concomitant effects, all of which were totally disregarded by Iakovlev and are readily available in the open literature. For example consider the writings of Dr. Susan Lester, a Harvard pathologist, in the **Manual of Surgical Pathology** with respect to this issue. Dr. Lester's credentials include Assistant Professor of Pathology Harvard

Medical School, and Director, Breast Pathology Services, Brigham and Women's Hospital Boston, Massachusetts.[239]

Dr. Iakovlev's October 6, 2014 Report regarding the Patient 3 matter is little different from his prior reports I have discussed above. His opinions and conclusions expressed in the Patient 3 report suffer from the same problems as explained above.[240]

Response to Iakovlev's April 24, 2015 Report

In the April 24, 2015 Expert Report Iakovlev once again speaks to the issue of polypropylene degradation although he readily admits he is not a material scientist.[241] His selection of references ostensibly to support his thesis does not, in fact, do so. For instance, (page 9) he writes "Liebert, et al found "polypropylene will degrade *in vivo* over time if not adequately protected by antioxidants." However, he chooses to omit that Ethicon's Prolene is not just polypropylene, it is formulated polypropylene with added ingredients, two of which are effective polypropylene stabilizers. Liebert's article states emphatically "Infrared spectra and mechanical testing of implanted and non-implanted filaments containing an antioxidant show no change in chemical or physical properties as a result of implantation."

I have previously responded, in this report, to Iakovlev's apparent adoption of data and hypotheses of Celine Mary, Costello, Clave and Wood on the matter of Prolene degradation.

The Iakovlev statement (page 10, April 24, 2015) "Environmental stress cracking and/or oxidative degradation facilitated by macrophages have been found to be the most likely mechanisms to explain polypropylene's *in vivo* degradative processes" has no basis in fact. The statement is followed by 16 references, none of which possess any quantifiable data substantiating/confirming Iakovlev's stated opinion on Prolene degradation by ESC. I have responded to ESC as it relates to polypropylene earlier in this report (page 21-22)

That Iakovlev likens the environmental conditions of Prolene explants and their *in vivo* response to that of an exterior environmental exposure (April 24, 2015 report) confirms his lack of understanding of material properties, and their relation to use environment (see Iakovlev references 448 and 467). The former report is on the effects of polypropylene in artificial and sunlight exposure while the latter relates to *in vivo* conditions. Prolene implants are not exposed to ultraviolet light *in vivo,* with the exception of ophthalmological sutures. It is important that the latter, Sternschuss, et al., manuscript is a review of a myriad of articles and espouses the authors opinions. They performed no independent laboratory work and data therefrom. Numerous statements therein are without sound scientific data. As an example, consider the following:

- "Generally we have no idea of exactly what was used in a particular mesh construct." Yet they are freely opining on the properties of Prolene and its material composition.

- "After implantation PP mesh absorbs certain substances from bodily fluids, notably cholesterol and fatty acids, which could alter the physical and mechanical properties of the mesh." They are right, yet apparently do not understand why. Their implication is that absorbed materials will adversely affect physical properties, yet Burkley's 7 year dog study proved otherwise. His data showed overall improvements in physical properties such as elongation and toughness. These property enhancements can be ascribed to well-known plasticizing and toughening effects of fatty type materials found *in vivo.*[242,243]
- Finally, the Sternschuss, et al. manuscript was poorly written and data documented that it elicited a lengthy letter to the editor. The following rebuttal quote describes this article in generalities very well, i.e. "We believe this article is biased and contains multiple statements that are poorly supported by quality science" and "statements with partial truth include results from the article by Clave et al taken out of context." For example, the authors emphasize oxidation during processing and then after implantation. However, Clave made statements their analysis was unable to confirm oxidative damage of implanted mesh leading to degradation. This very important statement was omitted by Sternschuss and co-workers.[244] The Letter to the Editor is critical of the author's reliance on Clave's writings noting finally that "Clave could perform chemical analysis on only 32 of 84 explants, which is too small a sample for an appropriately powered study." Moreover, the title of the Clave, et al. study "Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants" is very misleading.

Iakovlev continues his so-called degradation discussion (page 10) and states, "Ethicon's internal documents, was used by Ethicon's scientists-along with histological methods-to characterize the physical properties of explanted Prolene sutures which, as discussed in detail below, lead Ethicon's scientists to conclude that the cracking observed on the surface of Prolene is the polypropylene and not proteinaceous." However, this mis-states the facts of the Ethicon documents. For instance, ETH.MESH-15955438 describes B. Matlaga experiments of March 23, 1983 wherein Prolene explants ranging in *in-vivo* residence times from 2.5 to 7.0 years, and fixed in formalin, were examined by light microscopy and polarized light. It was noted that 3 of 5 explant samples showed no cracking. It is important to note that no mention was made if the samples were dry or wet when examined, but all were fixed in formalin. Ethicon documents of March 29, 1983 (ETH.MESH 1595544 thru 15955440-15955442) continued with examination of Prolene sutures used to secure a Dacron graft. The formalin fixed Prolene sutures were not cleaned in any way and thus necessarily contained adhered, formalin-fixed flesh. The Histological Evaluation (page ETH.MESH 15955442) stated "No endothelial cells were present on what was judged to be the luminal surface. Only one cross sectional profile of PROLENE was contained in this slide. No evidence of cracking was noted." One sample only was available for testing of tensile strength and gave 54% of its pristine value; however, at least 5 tests are required for statistical validity and damage of the suture could not be explained.[245] Moreover, no strain or elongation test data was collected thereby not allowing suture toughness to be determined.

On March 25, 1983 Emil Borysko, an Ethicon scientist, provided data on "sutures explanted after 2 to 6 years implantation (ETH.MESH 15955453-15955454)." Nine samples were submitted for evaluation, three were stored in Formalin from their time of explanation, and the remainder had been allowed to dry. The uncleaned samples were examined microscopically. In essence, the results confirm most of the dry samples showed some cracking and the wet samples were essentially free of cracks. The wet samples were allowed to dry, and then examined. The General Observations and Conclusions of this report are as follows:

- Sutures kept in the wet state do not exhibit cracks
- Upon drying, cracks appear-this was actually observed happening by drying "83-165 6 yr. wet" on the microscope stage."
- The work of Dr. Peter Moy is further support for the work of Dr. Borysko (see ETH.MESH 00006325) wherein wet explants, even though fixed in Formalin, are far less likely to crack than dry explants.

It is puzzling that Iakovlev would reference the 1984 Ethicon Matlaga report (ETH.MESH 15955462-15955468) as part of his "degradation" theory as she describes the following:

- Six Formalin fixed tissue samples of Prolene sutures were evaluated without cleaning
- Sutures were kept wet and examined by light microscopy while wet and dry
- Samples 1-5 showed no surface cracking in light microscopy examinations (ETH.MESH 15955462) as sutures or histological sections.
- Sample 6, a 7 year explant, showed surface cracking
- The average breaking strength (tensile strength) for the size 3-0 Prolene was 76.5%, and for size 4-0 was 98.25%-elongation data were not collected.
- Only one sample was available for the 5-0, 7 year suture explant which showed 76% tensile strength retention.

Finally, even though the author notes "This breaking strength data must be viewed with caution since damage to strands during removal may have occurred despite efforts to prevent it," the tensile data of uncleaned samples, are quite good given the authors admonition. Once again, the data confirms, a simple but important concept, dry tissue is highly susceptible to cracking and plays no role in Prolene degradation.

The April 25, 2014 Iakovlev report continues to defy scientific and chemical principles by stating "Recently, degradation of polypropylene was detected using histological and transmission electron-microscopy approaches." One cannot confirm chemical composition and changes in chemical species and composition with dyes and microscopy as per Iakovlev. For instance, Iakovlev essentially defines degradation as "cracking" of the polypropylene surface, yet he has no scientifically valid means of identifying and confirming the chemical composition of polypropylene.

For instance, consider Iakovlev's beliefs:

- Polypropylene **does not** stain with H & E dyes. Polypropylene is birefringent
- Polypropylene responds to polarized light because it is birefringent
  With this said, consider what else Iakovlev testifies to:
- Collagen (proteins) **will stain** and polypropylene will not
- Collagen (proteins) are birefringent as is polypropylene
- Collagen (proteins), because it is birefringent, responds to Polarized light, as does polypropylene because it is also birefringent

With respect to birefringence and polarized light response, both Collagen and Polypropylene respond affirmatively. There are many birefringent compounds with varying chemical structure and composition that respond to polarize light.

However, while collagen and polypropylene both respond to polarized light, only collagen will stain, while Polypropylene will NOT stain; the perfect example of two very different chemical species but both being birefringent. Consequently, in the absence of FTIR spectroscopy or other chemical structure identifying tools one can only conclude that two materials, one accepting dyes, and one not accepting dyes are **different** in chemical composition; and they are. It is only with FTIR and other analytical tools can one specify the chemical make-up or structure of the two different compounds. My work with FTIR spectroscopy has made this determination and the composition of Iakovlev's "bark" has been confirmed as proteins, not Prolene or even degraded Prolene.

It is puzzling in the face of his beliefs Iakovlev writes the following in the International Journal of Medical, Health, Biomedical and Pharmaceutical Engineering, Vo. 8, No. 9, 2014. "A stand-alone finding was the detection of polypropylene degradation. The filaments in all (100%) of both lightweight and heavyweight designs showed a layer of homogeneous material surrounding the filaments. The material stained purple by H&E stain which was different from the clear filament core. To test if the material is synthetic the sections were examined in polarized light. Both the core and outer layer showed the same optical properties in polarized light. These findings indicated that the layer is degraded polypropylene. The degradation layer resembled a tree bark: it surrounded the filaments and showed cracking and partial detachment from the core." However, Iakovlev has stated repeatedly that polypropylene cannot be stained by H&E dyes and proteins do accept H&E dyes. Iakovlev's "bark" accepts H&E dyes and therefore simply cannot be polypropylene as he states in the referenced and published manuscript.

Iakovlev, with co-authors S. Guelcher and R. Bendavid published in "OFP-13 Joint Oral Free Paper Session IT in Pathology/other Topics, a writing titled, "In Vivo degradation of surgical polypropylene meshes: A finding overlooked for decades." Excerpts from the paper follows: "The degraded polymer formed a demarcated layer at the surface of the filaments similarly to a tree bark. The bark traps histological dyes due to its porosity and is easily visible by conventional microscopy. A number of findings confirmed that the bark originates from polypropylene itself and forms in-vivo. Conclusion: An easily visible by conventional microscopy, the finding has been passing unrecognized through pathologists' microscopes for decades."

- Once again he writes for the scientific community that "bark traps histological dyes due to its porosity," when he has repeatedly testified that polypropylene does not accept dyes. Moreover, well established scientific facts state clearly that staining can only occur as a result of a chemical reaction between and dye and, in this case, flesh.

- Consider the following:

  H & E dyes must react chemically with a material before the material will stain appropriately.

  The following information is taken from the "Chemistry of H & E Staining," published in *The American Journal of Medical Technology*, Vol. 40, Number 11, November 1974. "Many individuals with long experience in histology still do not completely understand the Chemistry of H & E Staining. Consider also, the writings of M. Lamar Jones, who published "Mastering the Trichrome Stain" in *Connection 2010*.[246] The article speaks of methods of staining, i.e. "At the onset it must be made clear that the methods control how ionized acid dyes react with the ionized basic tissues. This is the fundamental principle on which they depend and the explanation is only about how that fundamental reaction can be manipulated." "The components involved in histological staining are dyes and proteins. The fundamental process involved is the chemical bonding between the carboxyl groups of the one and the amino groups of the other."[247] "pH Control-Staining depends largely on the attachment of dyes to proteins. These have both positively and negatively charged groups."[248] Successful histological staining is all in the chemistry and not porosity as alleged by Iakovlev.

  Lester's Manual of Surgical Pathology describes the proper method of slide staining.[249] There are several steps for washing and blotting slides during the staining process in order to remove gross or unused stain. In none of the staining steps is substrate porosity mentioned, but proper sample pH to affect the chemical reaction is a central theme of the process. Warnings are made, i.e. "slides are left in xylene until over-slipped to avoid drying artifact that can make interpretation difficult or impossible." Given artifacts are typically defined as the unwanted effects of a process, fixation artifacts are "largely restricted to a few items such as deposits from the fixative or its reactions with tissue components, and the physical effects of fixation we would prefer to do without, such as detectable shrinkage, both at the gross and microscopic levels, the hardening of some tissues which causes chatters parallel to the knife edge; and the brittleness from some fixatives which results in shattering and cracking during sectioning."[250] This phenomenon is easily recognized in Iakovlev's Fig. JR-16a where it is obvious the approximate right one-half shows loss of adhesion between Prolene and collagen thereby offering the viewer a "side" view or an angle of observation. In contrast the approximate left one-half shows strong adhesion of collagen to Prolene and also loss of collagen cohesion thereby opening a void between collagen molecules. Consider also Fig. JR16B which is

> stated to be the same field as in 16a but under polarized light. This is a classic example of three birefringent materials and all appear with different color intensities and hues. Consider for instance, the central portion of the photomicrograph is known to be Prolene, and Prolene is known to be birefringent. The central layer of the photomicrograph is collagen and collagen is known to be birefringent, and finally consider the outermost portion of the photomicrograph said to be collagen, again birefringent. One must also consider the angle of observation for each segment of Fig. JR16B supporting birefringence for all. Since both collagen and Prolene are birefringent you cannot use polarization to make a chemical distinction between the two materials.

Figure JR17a is an excellent example of artifact construction showing clearly shattering of the collagen layer presumably during microtoming. For instance, in viewing the blue portion of the photomicrograph, labelled non-degraded core by Iakovlev, the viewer transitions to the ruptured collagen layer separated by paraffin (white area). This photomicrograph is an excellent example confirming tenacious adhesion of collagen to Prolene, and cohesive failure of collagen alone. This photomicrograph depicts an H&E stained sample wherein, and by Iakovlev's testimony, collagen stains pink, as is the case in Fig. JR17a. There is no degraded area; rather this photomicrograph depicts loss of cohesion of collagen and strong adhesion of collagen to Prolene.

> Fig. JR 18b, Identified by Iakovlev as being the same field as JR 18a, but under polarized light is stated by Iakovlev as an example of an artifact, i.e. via his statement, "In this field the non-degraded filament core detached from the slide during processing."
>
> This clearly represents an ideal example of artifacts generated during the staining process.

- He further states "a number of findings confirmed that the bark originates from polypropylene itself and forms *in-vivo*," yet he offers no such findings.

I have also reviewed Iakovlev's March 5, 2015 testimony in the Bellew litigation and the following responses are helpful to fully and completely understand Iakovlev does not understand the chemistry of staining or chooses to ignore it.[251]

> Mr. Anderson, Question: What is the significance of that cracked outer layer that we're seeing in 1910-G?
> Answer: This is the bark layer or outer layer of the degraded polypropylene. It's the same wood but because it was exposed to the outside environment, it's all cracked. It has all these crevices, cracks, and cavities. The same thing happens with the polypropylene. When it's exposed to the body environment, it cracks and forms these cavities, and the histological dye, it gets trapped in it so it sticks in between. It's like clothing. The dye gets in between the fibers in the clothing and that's why it stains. The non-degraded polypropylene is solid, so it cannot be stained."[252]

When cross examined by Mr. Thomas why polypropylene was not stained by H&E dyes, he again answered that "polypropylene is solid, so it doesn't have cavities to trap dyes." When asked if "Isn't it true that typically an H&E stain, hematoxylin and eosin stain leaves their colors by a chemical reaction?" he responded "Not exactly chemical reaction. Most of the dyes are trapped... So, it's not fully chemical reaction when molecules form new molecules. It's more of a trapping or binding of the dye molecule inside the material." Thus, given his statements, it is absolute that Iakovlev does not understand the chemistry of staining yet his entire theses of degradation is based on an incorrect assumption that "degraded Prolene" stains.

His testimony that (1) he does not know if polypropylene possesses a charge or not, and (2) admission he does not know if the reason polypropylene does not accept dyes is due to the fact polypropylene is not charged,[253] again is absolute confirmation of his lack of knowledge of the staining process for which he has and continues to make invalid and unsupported statements regarding Polypropylene's properties.

He provides an analysis of his exhibit P-1910G in part by the printed designations on the photomicrograph. It is instructive that Iakovlev has testified the clear areas of such slides are wax where there is no flesh or Prolene. Other sections of the H&E stained slide are pink to blue-purple; a portion of which Iakovlev labels as Collagen. However, Iakovlev also has labelled a portion of the slide as "Degradation bark," and this so-labelled "degradation bark" is stained pink-blue-purple, precisely the colors one would expect of proteins! It must be remembered that Prolene will not accept dyes, and proteins will readily accept dyes, therefore Iakovlev's dye accepting "degradation bark" as labelled cannot be of Prolene origin, but rather from proteins.

Furthermore, P-1910M is an excellent example of the type effects light manipulations can produce. For instance, Collagen, wax and a portion of Prolene all show identical polarization effects by completely blocking the light path.

Iakovlev fails to testify about P-1910-O, a trichrome stain photomicrograph. This photomicrograph confirms adhesion of Collagen and other proteins to Prolene therefore defeating the idea of "degradation bark." For instance, Iakovlev has testified the green color represents Collagen, and it is known that cytoplasm, fibrin or muscle are pink-red.[254] The photomicrograph confirms adhesion of a stained and Formalin-crosslinked protein coating to Prolene, and is not degraded Prolene.

Photomicrograph P-1910-U speaks to the absence of calcium in tissue but as importantly to the consistent staining and identical color of Collagen and the protein layer, i.e. the protein-formaldehyde coating.

I have also reviewed the Iakovlev report of May 22, 2015
RE: Mr. Donald Iholts, hernia mesh excision

Much of the report is included in other Iakovlev documents I have read. Therefore my comments will focus on specific issues of interest as related to his past testimonies and new comments included in the May 15, 2015 report.

Iakovlev continues to emphasize Environmental Stress Cracking and identifies it as the most likely mechanism for his proposed polypropylene's degradation by his page 8 statement, i.e. "Environmental stress cracking and/or oxidative degradation facilitated by macrophages have been found to be the most likely mechanism to explain polypropylene's *in vivo* degradation processes."[255] However, the multiple sources in scientific literature explicitly refute this tenet.[256,257,258,259,260] Moreover, he continues to cite references not germane to the present instance; see his reference 448 dealing with artificial light and sunlight exposure of polypropylene.[261]

Iakovlev continues to stress the supposed importance of cracks and cavities to the staining process (Figure Set 12a) and ignores artifact creation and the chemistry of H&E and Trichrome staining.[262] Figures Set 12a confirms both Hematoxylin and Eosin have exerted their color producing stain of the protein-formaldehyde composite shell surrounding the Prolene fiber. Iakovlev continues to ignore his own admonition that PP cannot accept H&E stains.

Figure set 13a[263] is an excellent example of the interface of Prolene and the adsorbed protein coating wherein Iakovlev's arrows confirm excellent adhesion of proteins to Prolene as seen through an angled view, thereby allowing dye particles of Prolene to be seen through a thin protein layer. Figure Set 14a of trichrome staining confirms the presence of protein/collagen (light green) and cytoplasm, fibrin and muscle (red).

Figure Set 17 of Von Kossa calcium stain is instructive in its tissue staining consistency and artifact formation (cohesive failure of tissue).[264]

Iakovlev presents Figure set 22 wherein he states "Mesh filaments show cracking immediately after excision, before the mesh is placed in formalin or before the tissue is allowed to dry."[265] However, on close examination Figure set 22 is described as "Freshly excised TVT sling after 9 years in the body, washed in saline and tissue-free filaments at the mesh edges are photographed immediately after excision (no contact with formalin and no drying), regular light microscope, 20x objective, cropped image." One knowledgeable in the discipline must ask "how can the filament be tissue free if it has not been cleaned in any way?" In my opinion it cannot as it is well-known that protein coatings form immediately with fiber/mesh implantation to form a tenacious bond between the hydrophobic Prolene and collagen.[266] Therefore, tissue must be present given no cleaning was performed before microscopic examination. The topic of tissue cleaning, and fixation has been discussed extensively by me in this report and will not be repeated.

Iakovlev's Figure D119a is an excellent example of artifact formation, and mis-assignment of H&E stained collagen which Iakovlev has labelled "degraded polypropylene."[267] His so called "degraded polypropylene" stained blue in regular light,

while it is well established that polypropylene cannot and does not accept dyes given its non-polar chemical structure. It is also well known that collagen (proteins) readily accept H&E stains, as they have in Figure D119a. Also note the artifact formation with cohesive losses of collagen. Figure D120a is yet another example of extensive artifact formation confirmed by collagen cohesive failures and rupture of the collagen-formaldehyde composite.

Iakovlev's Figures D121a and D122a of Trichrome stain are yet other instructive and helpful photomicrographs. Note the arrows of both point to Iakovlev assigned "degraded polypropylene."[268] Note too that in each, the stain colors are red and green and Iakovlev assigns these as "degraded propylene." Iakovlev assignments are inconsistent with published works who state that "Cytoplasm, fibrin, and muscle stain RED, while Collagen stains BLUE or GREEN. Jones also writes that "At the onset it must be made clear that the methods control how ionized acid dyes react with the ionized basic tissues. This is a fundamental principle of which they depend and the explanation is only about how that fundamental reaction can be manipulated." The article continues with "When the protein component of a tissue is exposed to a fixative agent an interaction between the protein chains and the fixative occurs. Usually a 3 dimensional, insoluble protein "network" is formed." Given the fundamental principle of trichrome staining, is "how ionized acid dyes react with the ionized basic tissues" polypropylene cannot react with trichrome stain. Polypropylene has no acid or basic components and thus no pH. Given these irrefutable scientific facts, Iakovlev's assignments of degraded polypropylene are in error.

I have reviewed Iakovlev's Richard Schmidt report dated March 9, 2015[269] and have the following comments:

Much of this report is identical to others Iakovlev has written. Thus, there will be some redundancy herein.

Figure Set 12a. is titled "Degradation layer (bark) has microcracks and microcavities which retain histological dyes (regular light upper panel), however has the same optical properties (birefringence, bright in polarized light, lower panel) as the non-degraded core, H&E, 100x objective with oil immersion."[270]

Once again it is clear that Iakovlev clearly does not understand the chemistry of histological dyes from which he is drawing sweeping and erroneous conclusions. Consider Iakovlev's continuing statements on microcracks and microcavities; these are in large measure unimportant and do not control the dyeing process. While cracks and cavities allow dyes to wet or come in contact with more surface area than a non-porous media, the dyeing process is clearly one of a chemical reaction between the H & E dyes and proteins, nucleic acids, cytoplasm, collagen and a variety of proteins. When the chemical reaction occurs, the dye is chemically bound to the tissue it stains and cannot be washed away in the subsequent slide washing step of the histological staining process. Washing is used in the staining process to wash away EXCESS dye(s) that did not chemically react with human tissue. PP will not, and cannot, react with H&E dyes!

Therefore, PP does not and cannot be changed in color by H&E dyes. Thus, any material that is dyed or accepts color during the staining process must originate from human flesh. This is seen in many, many occasions of Iakovlev's work. Consider, for example, Figure Set 12a;[271] it is well know that Eosin reacts with positively charged species and in the process produced a pink-red color. We see that in the upper-right slide where the pink color is labelled collagen. Intermingled within the collagen is the blue-violet color of Hematoxylin dye (H), and the area Iakovlev has labelled as degraded bark. However, this is a mis-assignment in that PP cannot accept dyes, and thus cannot be colored. The proper assignment is that the Hematoxylin dye has reacted with proteins (collagen + Formalin in this case) and in the process the well-known blue-violet of Hematoxylin dye is formed. Notice Iakovlev assignment of the so called, non-degraded core, which is NOT stained. It is PP and PP cannot be stained by H&E dyes. Therefore, the mere fact that the "Iakovlev labelled degraded polypropylene" stains blue is absolute proof his assignment is incorrect. Thus, his conclusions and opinions are not based on well-known chemical principles of H&E dyes are therefore, in error.[272] In Figure Set 12b Iakovlev shows a histological slide wherein the filament core is detached from the surrounding tissue and is not present.[273] The very next Figure Set 13a however, shows the filament core and the detached surrounding flesh. Note the H&E stains of violet and pink confirming presence of proteins and DNA/RNA. It is clear in both the two photomicrographs that the angle of observation of the slide allows one to observe the cut surfaces of flesh and PP filament to be in different essentially parallel planes. In other words, the surface of the PP filament fiber disc is above the surface of the surrounding adsorbed protein layer. Consequently, a side view of the PP disc is in view and one can readily see the blue granular pigment of Prolene.

In Figure Set 13b[274] there is yet another mis-assignment as Iakovlev again speaks of a degradation area but it is well known, and admitted by Iakovlev, that PP does not stain. Thus, if PP does not stain, how can his assignment of degraded PP be seriously considered. It is well known that Formalin and Collagen (proteins) form hard, brittle surfaces and since their makeup is of proteins, they do accept dyes and color.

Iakovlev's Figure Set 14a of Trichrome stain once again clearly delineates his concept of staining relies on porosity/microcavities and not the chemistry of dyes and proteins.[275] From a very simplistic perspective, how can one possibly rely on a physical phenomenon of porosity to identify the chemical composition of a material?

Iakovlev's Figure Set 14b of a Trichrome stained slide labels green and pink colored materials as "degraded polypropylene" when it has been shown and he has written that PP does not accept dyes.[276] Moreover, the chemistry of Trichrome stains clearly states the Trichrome process stains cytoplasm, fibrin and muscle RED and collagen GREEN.[277]

Iakovlev's Figure Set 17 for Von Kossa Calcium Stain readily affirms the precepts I have set forth.[278] For instance, all the stained materials are shades of pink-red. Likewise, it is clear the area where the two black arrows are pointed is a very good example of flesh in contact with the filament being essentially identical to all other segments of the slides

flesh. In other words, there is no difference in the stained tissue in contact with the PP filament and that within the body of the slide and away from the tissue-filament juncture.

Iakovlev's Figure Set 18 confirms what one would expect. For instance, when PP is immersed in Formalin no chemical reaction occurs given no proteins (flesh) are present.[279] However, what will occur is extraction of antioxidants and UV absorbers by formaldehyde.

Figure Set 19a reaffirms Iakovlev's self-contradiction; For instance, he states, "Note that the degradation layer (bark) lost its ability to retain dye after melting. It melted together with the non-degraded core."[280] PP is a thermoplastic polymeric material that can be melted repeatedly without damage to the polymer itself. Thus, the original and non-melted PP fiber will not accept a stain and be dyed and neither will PP that has been melted. Consequently, if it did not retain dye after melting, it would not retain dye before melting; and, we know that to be true. Iakovlev's contention that the so called "degradation bark" lost its ability to retain dyes after melting once again confirms his lack of understanding of PP and of the histological dyeing process, and his gross error in writing and publishing "degradation bark" is PP.

Iakovlev's Figure Set 20a[281] dealing with Transmission Electron Microscopy of "A Specimen of Explanted transvaginal mesh" will not be discussed herein given my uncertainty of the mesh manufacturer.

Iakovlev's section for Richard Schmidt on Polypropylene Degradation should be dismissed for lack of credible data and expertise from which to draw material science conclusions. He has readily admitted he is not a "Material Scientist" yet he continue to opine on Material Science issues, with no credible data.

Iakovlev's Figure RS-24a is yet another example of artifact formation and again mis-assignment of a "degradation layer" as PP.[282] Iakovlev has once again identified Hematoxylin and Eosin stained tissue as degraded polypropylene

I have further reviewed the May 23, 2015 Expert Report of Dr. Vladimir Iakovlev re: Paula Carole Clowe and have the following observations.

Dr. Iakovlev's writings leading up to the examination of Histological images are essentially with other reports he has written. However, his FIGURES of histological slides are of interest and I will respond to some of his finding particularly when he refers to Prolene degradation. Figure 7a, page 31, clearly shows artifacts of slide preparation with tissue separation. Note the H&E stained bio-film layer attached to and surrounding the Prolene filament. One must remember that H&E stains will not stain PP but will stain collagen and other proteins, as we see in slide 7a. The polarized photomicrographs show two most important features of polarization; i.e. slight polarization of the protein layer as it contains Collagen, a birefringent material that polarizes light as is seen, and the varied colors of Prolene and the protein layer showing the effects of light

impingement during the polarization process. Iakovlev is in error characterizing the protein coating layer as degraded polypropylene.

He continues his mis-assignment on page 32, Figure 7b. The H&E photomicrographs (top) show blue-pink stained material (remember, Collagen and proteins) which cannot be Prolene given they are NON-STAINABLE by H&E dyes. The polarization photos (below) are consistent with this tenet given collagen (protein) is birefringent and polarizes light. It appears the collagen and remainder of the slide is in a different vertical plane.

The photomicrographs on page 33, Figure 7c are perfect examples of mis-assignments. It is questionable whether the two top photomicrographs are at the same magnification (100) and the two bottom ones. The top ones are examples of Prolene and strongly adhered collagen-proteins. Remember, proteins are colored by H&E dyes and Prolene is not. Thus, it is clear that the assignment given is incorrect. The higher bottom view at a higher magnification is much easier to confirm tenaciously adhered protein coating to Prolene. The “adhesion line” between the proteins and Prolene is very “tight” and void of any loss of adhesion. Note that Iakovlev himself has assigned the red portion as tissue and blue portion as non-degraded core. However, I am puzzled by and with his mis-assignment of the tissue-Prolene interface as degraded Polypropylene? The photomicrograph represents an excellent example of an almost “picture perfect” adhesion interface.

Figure PC9 is an example of Prolene and the remaining slide portion existing on separate planes.

Figure PC14a is an excellent example of artifact formation during histological slide preparation. For instance, note the separation of collagen layers (cohesive failure) confirmed by wax separation, and the interface of collagen and the protein coating layer (adhesive failure). The right lower portion of the photomicrographs confirm beyond any doubt that the protein coating layer was intimately bonded prior to artifact formation. Significant separation of biofilm and collagen can be seen at the top most positions of the photos. Close examination of Figure PC14b (polarized light) confirms the protein coating layer and the intact adhesive bond (lower right) as in “regular” light.

Figure PC15 shows both “regular (left) and polarized (right)” light. One can easily confirm a protein coating layer interface in regular light due to H&E staining.

PC-16a, 16b, 17a are examples of protein adhesion to the Prolene interface with some influence of the slide making process. Note the protein coating layer-Prolene interface has been stressed and consequently has weakened the interface. This is supported by Figure PC18a where trichrome stain was used in regular and polarized light. The Trichrome staining process stains Collagen green, and cytoplasm, fibrin, and muscle RED; exactly as depicted in PC18a. Given these color designations, artifacts formed whereby we can see cohesive failure of collagen (green) but excellent adhesion of collagen and the remaining protein coating layer composition of cytoplasm, and/or fibrin

and/or muscle (all of which make up the protein coating layer composition). This photomicrograph is an excellent example of how slide preparation can dramatically affect tissue and its orientation. It is also an excellent proof example that Prolene does not degrade *in vivo.* It further confirms that those promulgating Prolene degradation *in vivo* simply do not understand or wish to ignore basic facts of chemistry and the staining process. The polarized sample (Figure PC18b) is an excellent explanation and example of how polarized light is limited in value when examining explants. For instance, the "regular" light photomicrographs on page 76 absolutely confirm the presence of a protein coating layer and the adhesive tenacity of collagen to cytoplasm, fibrin, and or muscle. However, Dr. Iakovlev has identified a protein coating layer in regular light as the "degraded layer" in Polarized light (PC18b). These two tenets are contradictory, hold no scientific merit, and should be disregarded.

Similar errors are made by Iakovlev with respect to Figure PC-19a (regular light) and -19B (polarized light). Iakovlev continues to ignore the chemistry of staining for nanocavities and porosity; totally disregarding the chemical reactions that must be affected between the stains and acid or basic materials.

In summary, Dr. Iakovlev is simply missing or chooses to ignore the fundamental chemistry that control dye staining. The chemistry of dye stains has been discussed earlier and in detail in this report and will not be repeated at this point. Therefore, Dr. Iakovlev's opinions regarding Prolene degradation are simply wrong; I have seen no compelling scientific evidence that Prolene degrades *in vivo,* and my opinion is that it does not. There is compelling evidence to support that tenet and that evidence has been included and discussed in this report.

Now we will consider Iakovlev's writings with respect to Patient 4:

- Consider Iakovlev's Figure 7A (upper left and right photomicrographs) where one sees more artifact generation by shattering of the interface between collagen and Prolene.[283] The core (upper 7A) does not respond to H&E dyes as is shown. Thus the core has not reacted with dyes and consequently no dye color is generated, as we know to be the case with polypropylene or Prolene.
- The upper identical right photomicrograph has labelled areas delineated by Iakovlev as, a "degraded bark" and "collagen" (upper right). Note that <u>both</u> the designated "collagen" and the so-called "degraded bark" have reacted chemically with H&E dye, developed color, and thus are composed of protein(s). One must remember Prolene cannot chemically react with dyes and no color is produced, but collagen reacts with H&E dyes and is dyed pink. Note the delaminated layer of collagen. However, in contradiction to his writings Iakovlev insists that the so-called "degraded bark" is polypropylene. If that were so, the so-called "degraded bark" would NOT accept dye as polypropylene does not accept H&E dyes, and accordingly this stained material "CANNOT" be degraded polypropylene. Instead, it is collagenous (proteinaceous) material that has lost adhesion to the Prolene surface during explanting and subsequent staining, dyeing and manipulation.

- The variation in birefringence is readily explained by concentration differences of collagen. This concept is repeated on Iakovlev page 34.[284] View the "pink" areas of collagenous material; the pink protein (collagen) areas vary in intensity due to concentration and this concept is mirrored in the lower polarized light exposures. Note the light pink areas in the upper photos (proteins stain pink with H&E dye) and how they are manifested as blue color due to their birefringence (collagen is birefringent).

- Figure 7b[285] once again confirms error in Iakovlev's tenet. Viewing the upper two photomicrographs it is obvious artifacts have formed. Consider the cohesive rupture of collagen confirmed by the interior white areas while considering also the red-to-pink stained areas confirming proteinaceous material; not Prolene. Transition now to the lower photomicrographs (polarized light) and note the same pink segments from above are now responding to polarized as show in the lower photomicrographs. The materials can only be proteinaceous in nature and not degraded Prolene given both Prolene and collagen will respond to polarized light but of the two, ONLY collagen will stain pink!

- Figure 7c[286] (Iakovlev) is yet another example of artifact formation, and H&E staining proteins (pink color) adjacent to the Polypropylene surface.

- Iakovlev's Figure 7e[287] should be disregarded in its entirety given his reliance on micropores/microcracks for staining rather than chemical reactions between flesh and dye.

- Iakovlev's comments regarding Figure 7f[288] are in error and should be disregarded in its entirety. For instance, the material has been Formalin fixed and in such a state is water insoluble as it is no longer proteins alone but a water insoluble, brittle, protein-formaldehyde polymer.

- The statement associated with Figure 7i[289] is illogical and there is absolutely no data to support the contention that "it was present before surgery." Note that the melted product is white, as is the filament core. Prolene is a thermoplastic material and will melt and flow under sufficient heat and will retain its color and composition. Thus, Figure 7i simply shows "filament core" that has been melted under cautery and flowed beyond its spherical fiber confines as would be expected.

- Figure 8 of "New mesh manufactured using blue and clear filaments after exposure to formalin, H&E, 100x objective with oil immersion"[290] is helpful from a comparison purpose. For instance, Iakovlev has repeatedly fixed arrows on the periphery of Prolene and pointed out what appears to a "fuzzy" surface as is shown herein. It is obvious therefore, given this photomicrograph and the absence of any flesh and collagen, that his prior conclusions regarding degraded bark can be explained by microscopy aberrations as he has shown in Fig. 8.

- Figure 9a-9e[291] are transmission microscopy data for a non-Ethicon product to which I will not respond.

The significant and extensive volume of incorrect and unsupported conclusions, and lack of chemical controls by Dr. Iakovlev proves he has used fundamentally flawed methodologies in his mis-characterization of Prolene.

I have reviewed the July, 2015 paper entitled 'Degradation of polypropylene *in vivo*: A microscopic analysis of meshes explanted from patients'.[292] This paper purports to prove degradation via staining of polypropylene meshes based solely on microscopic techniques. There is no chemical evidence of any degradation and the stain methodologies utilized are not based on sound, scientific principles and experimentation. Polypropylene does not accept stain.

Review of Dr. Scott Guelcher's Oxidation Study

I have reviewed FTIR, SEM, and XPS data collected by Dr. Scott Guelcher in which he attempts to oxidize a polypropylene standard and TVT mesh with a mixture of cobalt chloride ($CoCl_2$) and hydrogen peroxide (H_2O_2). Even though this method is reported to be an aggressive oxidation environment[293] NO OXIDATION of any TVT devices could be determined by FTIR and XPS, and thus supports my contention that Prolene is a highly stable molecule and does not oxidize or degrade *in vivo*. Limited oxidation is shown in only two polypropylene control samples which do not contain antioxidants, unlike Ethicon's TVT device properly formulated with two, highly effective antioxidants.

The FTIR spectra of Figure 20 are taken from Dr. Guelcher's data collected during his cobalt chloride ($CoCl_2$) and hydrogen peroxide (H_2O_2) oxidation experiment, and supports my opinion that Prolene is resistant to oxidation. For instance, no carbonyl groups were formed during the oxidation experiment and confirms the exceptional stability of Prolene to an oxidation environment. The spectra below in Figure 20 show the 4 week polypropylene (PP) control sample (blue spectra) overlaid with the 4 week TVT sample (red spectra). Dr. Guelcher reports oxidation of the un-stabilized PP sample evidenced by the peak at 1736 cm^{-1}. However, no such peak is present in the TVT sample subjected to the same oxidation medium.

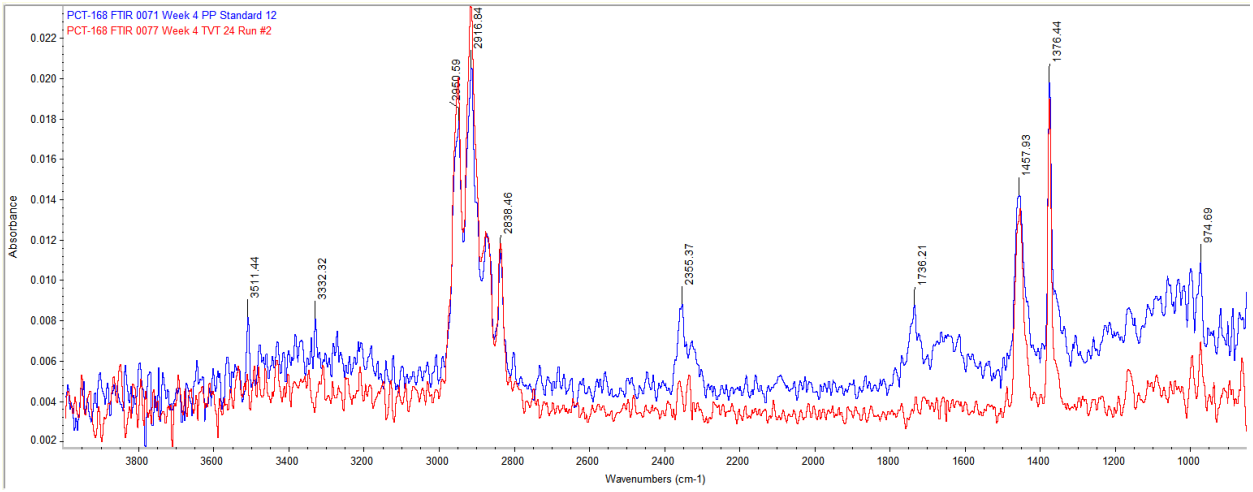


Figure 20. FTIR overlay of PP standard and TVT sample after 4 weeks in $CoCl_2/H_2O_2$.

Dr. Guelcher further opines in the article entitled Oxidative Degradation of Polypropylene Pelvic Mesh In Vitro,[294] that oxidation is present based on an FTIR spectrum of TVT at 5 weeks, however no 5 week control spectrum is provided. His experimental data is not provided in sufficient detail to prove these claims.

My inspection of his SEM photomicrographs suggests that the fibers were surrounded by deposited chemicals as their appearance is far different from the work of Dr. MacLean of Exponent.[295] Moreover, his manuscript was void of any experimental efforts to remove the oxidation medium from the fiber surfaces. Simply rinsing in DI water is not sufficient. Dr. Guelcher's SEM analyses are likewise inconclusive, as they show nothing indicative of TVT mesh oxidation. While there are some contrast variation of the individual fibers surfaces, these are likely the results of $CoCl_2/H_2O$ deposited residues on the fiber surface during the drying step, in preparation for SEM analysis. These deposits could have been easily characterized by energy dispersive X-ray (EDS) analysis while being imaged in the SEM, but no such data was provided. In addition, the data set continues through a six week period for TVT samples, while the polypropylene control experimentation, and thus data collection, is provided for only four weeks. This represents a flawed, inconsistent, and inadequate scientific approach when test specimens, and experimental controls are not subjected to the same time period and treatment regime. In any event, Prolene was not oxidized by the $CoCl_2/H_2O$ blend.

Dr. Guelcher's 'Methods' section regarding sample handling states that 'every week, 6 samples were removed, washed in DI water, and dried for analysis.'[296] Dr. Guelcher further notes that the samples were analyzed by XPS and FTIR in order to determine the presence of hydroxyl groups (-OH) and terminal C=O end groups.

Further analyses by X-ray photoelectron spectroscopy (XPS) analyses were performed in an effort to show Prolene oxidation. However, the experimental data does not support oxidation. The experimental data was collected by Dr. Bridget Rogers via

XPS.[297] A review of Roger's Table 1 XPS data (Figure 21) for TVT is clearly flawed and in error. For instance, all samples of TVT should exhibit carbonyl configurations (C=O) as Prolene possesses DLTDP and Ca-Stearate, both of which are carbonyl (C=O) containing chemicals. However, Dr. Rogers found only 4 of 17 samples showed C=O configurations. These data clearly confirms the methodology used is flawed and in error, given all 17 samples of TVT possess carbonyl containing chemicals, and consequently the XPS data should confirm the presence of C=O for all samples, but does not. That Guelcher used this analytical technique to confirm C=O presence is proof positive he does not understand Prolene's chemical composition, yet he is opining on its potential degradation tendencies.

Table 1. Fraction of carbon atoms bonded in the R-C-OOH and C=O configurations on TVT samples

	TVT					
Week	First Sample		Second Sample		Third Sample	
	R-C-OOH	C=O	R-C-OOH	C=O	R-C-OOH	C=O
0	0	0				
1	0	0	0	0.0135	0	0
2	0	0	0	0	0	0
3	0	0	0.0088	0	0	0.00180
4	0.0106	0	0	0	0	0
5	0.4874	0	0.5054	0.0062	0	0.0084
6	0.0051	0				

Figure 21. Bridget Rogers XPS Data for TVT[298]

Even the polypropylene control pellets subjected to this oxidation do not show a consistent trend in C=O detected via XPS (see Table 2, week 1 Polypropylene Standard data) as noted in Figure 22.

Table2. Fraction of carbon atoms bonded in the R-C-OOH and C=O configurations on polypropylene bead standards

	Polypropylene Standard	
Week	First Sample	
	R-C-OOH	C=O
0	0	0.0108
1	0	0
2	0	0.0209
3	0.0110	0.0169
4	0.0176	0.0396

Figure 22. Bridget Rogers XPS Data for PP Standards[299]

Patient Explant Analysis

I have testified in other mesh cases and hereby incorporate my prior reports and testimony.

In support of my opinions, I have examined Prolift and TVT Prolene explants from multiple patients and include excerpts from prior testing to visually and spectroscopically demonstrate the reasons for my scientific opinions, and I rely on the results of these analyses.

Analytical techniques used included Light Microscopy (LM), Fourier Transform Infrared Spectroscopy infrared microscopy (FTIR-Micro), and Scanning Electron Microscopy (SEM). At times other chemical analyses and techniques were used and in that case are included herein.

As previously stated, both Prolift and TVT devices are composed of Ethicon's Prolene mesh, a proprietary blend of polypropylene and additives. Pristine Gynecare Prolift Exemplar – Lot 3026838-120082 and Gynecare TVT – Exemplar – 810041B – Lot 3694576 devices, used as controls in my analyses, are shown in Figures 23 and 24 below. An FTIR-Micro spectral overlay of pristine exemplars is shown in Figure 25.

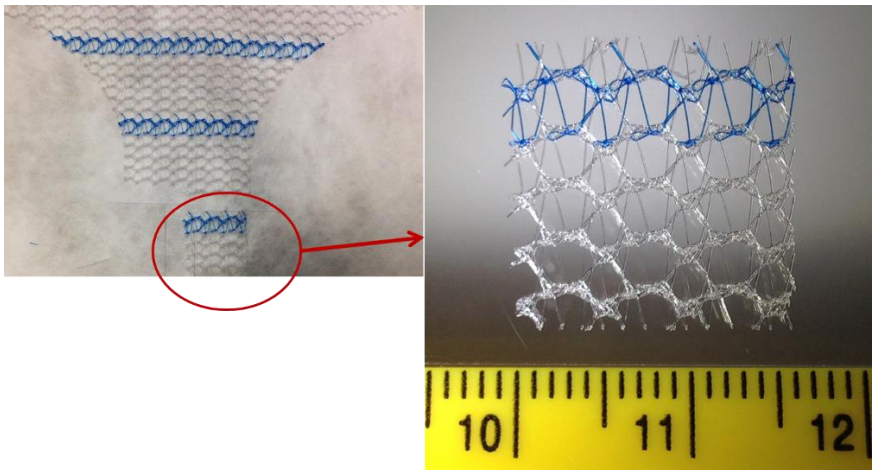


Figure 23. Pristine Gynecare Prolift Exemplar – Lot 3026838-120082

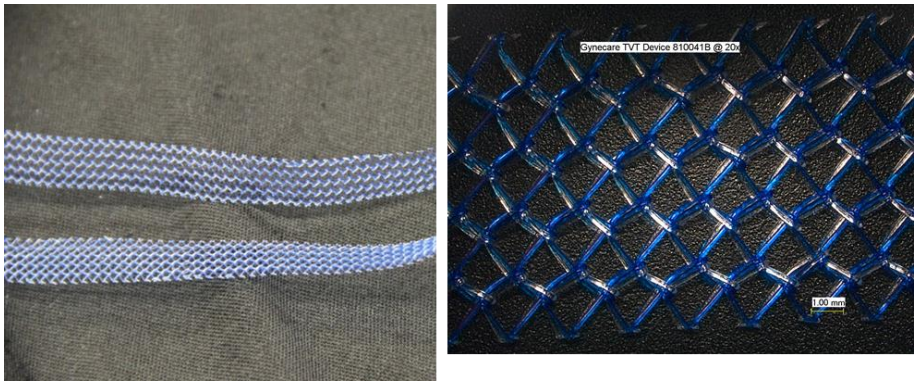


Figure 24. Pristine Gynecare TVT Exemplar – 810041B – Lot 3694576

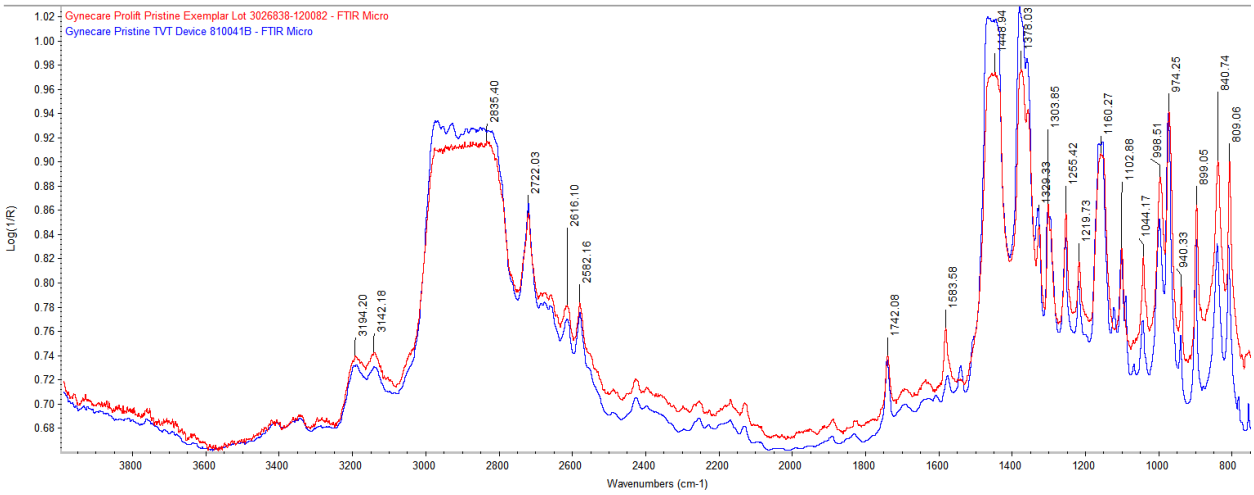


Figure 25. Pristine Gynecare Prolift Exemplar – Lot 3026838-120082 – and Pristine Gynecare TVT Exemplar – 810041B – Lot 3694576 – FTIR Microscopy

Some plaintiffs' experts have opined that spectral absorption at ~1740 cm^{-1} is solely indicative of oxidative degradation of Prolene. However, this spectral absorption is present in pristine exemplars, Figure 25, and represents the carbonyl group of DLTDP antioxidant of Ethicon's Prolene formulation. A reference spectrum of DLTDP is overlaid with a Prolift exemplar spectrum in Figure 26.

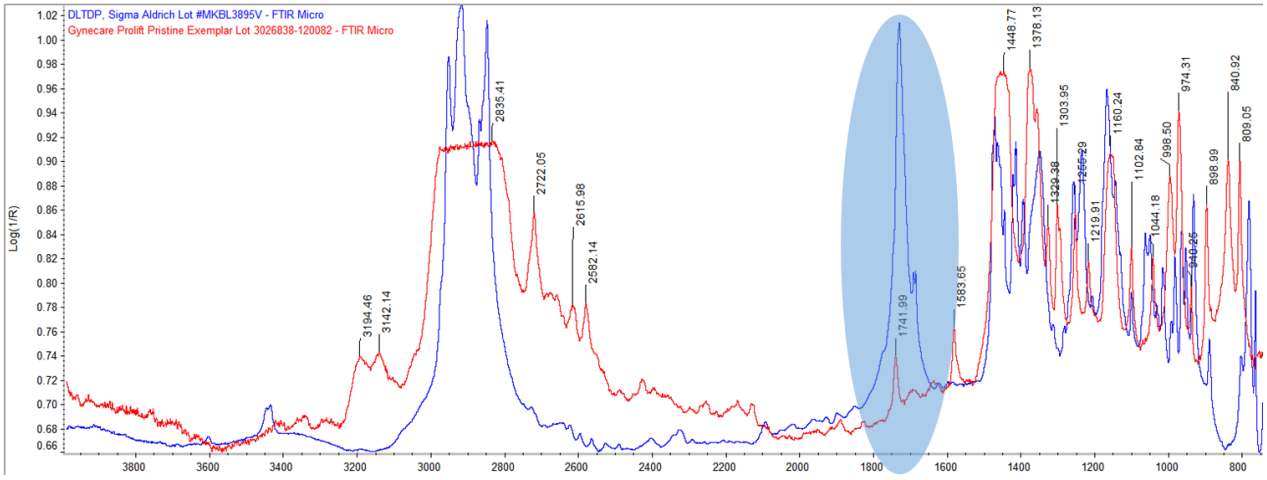


Figure 26. DLTDP overlaid with Pristine Gynecare Prolift Exemplar – Lot 3026838-120082 – FTIR Microscopy

An excellent example, and utility of SEM imaging, is provided in Figure 27 where the SEM image at 2,910X magnification establishes a thickness of 3.15 microns for the peeling surface layer of the adsorbed and fixed protein coating layer.

It is helpful in gaining a perspective of 3.15 microns to compare it to the thickness of a human hair, i.e. (Figure 28) at 69 microns.

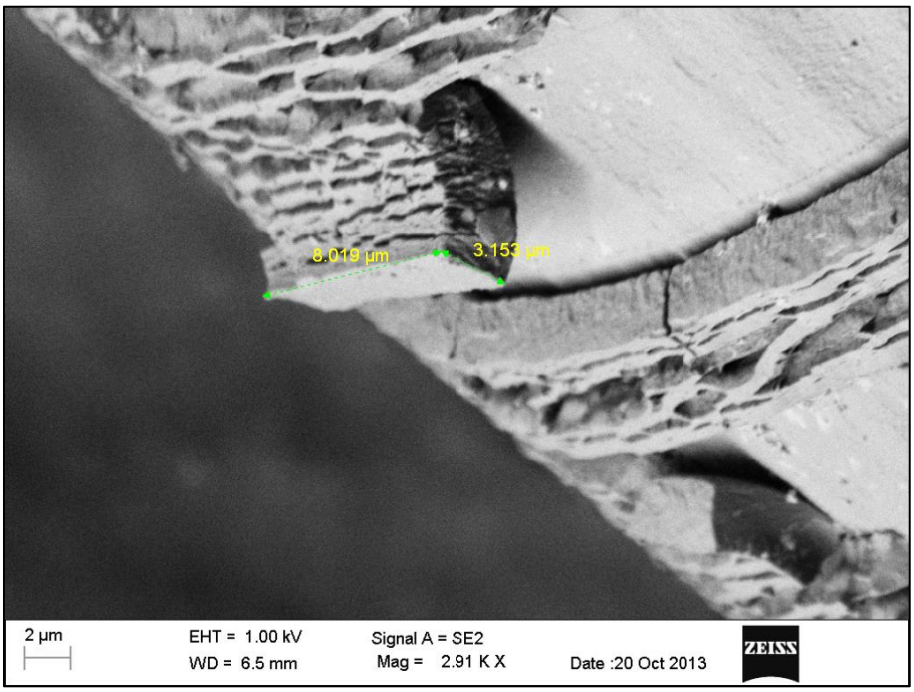


Figure 27. SEM Image of Patient 1 – Exponent Labs Processed Fiber

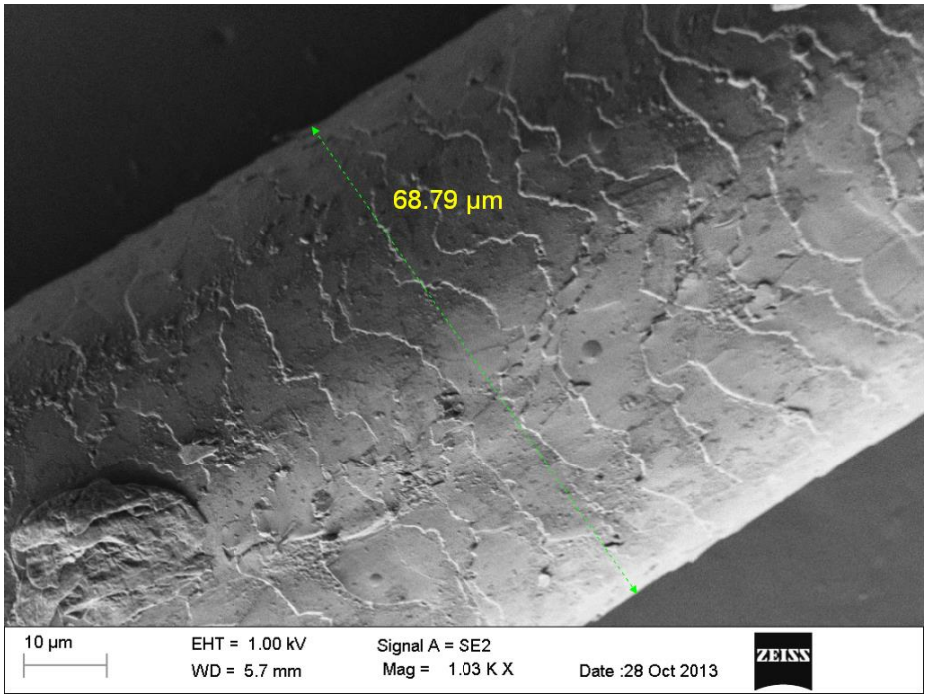


Figure 28. SEM Image of Human Hair

Therefore, the thickness of a human hair is approximately 22 times greater than the protein coating layer identified in Figure 27. Note also that the 3.15 micron protein layer is not an integral part of the smooth Prolene fiber whose extrusion lines continue to be present, are unmodified by implantation, and run perpendicular to the exterior surface layer. The lack of integration is obvious as shown by the dark shadow line representing a separation between the two layers, one smooth (Prolene) and the other rough (formaldehyde crosslinked protein coating layer). Certainly this would not be unexpected given the difficulty in removing the exterior layer. As the explant was maintained in formaldehyde subsequent to explantation, there was ample time and opportunity for formaldehyde to "fix" human proteins, thereby forming a protein-formaldehyde polymer sheath around the PP fiber(s) as shown, and adhere to the Prolene surface.[300]

At my direction, Dr. Kevin Ong of Exponent Labs received two tissue and mesh samples explanted from a patient, herein labeled as Patient 4 #1.1 and Patient 4 #2.1. The explants received were preserved in 10% neutral buffered Formalin. Dr. Ong divided the samples, rinsed and soaked them in distilled water, dried them once again and sent them to me via overnight delivery before any tissue removal or cleaning steps were undertaken. I received the 'before cleaning' samples labeled Patient 4 #1.1 and 4 #2.1, along with an exemplar TVT mesh (810041B, # Lot 3694576).

Upon receipt, Patient 4 #1.1 and 4 #2.1 samples were examined via Light Microscopy (LM), Fourier Transform Infrared Spectroscopy (FTIR), and Scanning Electron Microscopy (SEM). The initial data acquired were designated as "Before Cleaning" and recorded. The explants were returned to Dr. Ong with my request to clean the explants according to the cleaning process I developed (see Figure 29. Patient 4 – Exponent Labs Cleaning Protocol). After Cleaning according to Step #1 was affected the "1st Cleaning Step" explants were returned to me for further analyses. This process was repeated for the 5 cleaning step process already noted. Explant examinations were conducted at the following intervals:

- Before Cleaning
- After Cleaning 1
- After Cleaning 2
- After Cleaning 3
- After Cleaning 4
- After Cleaning 5

Sample Name	1st Step	2nd Step	3rd Step	4th Step	5th Step	6th Step	7th Step	8th Step	9th Step
Patient 4 #1.1 Patient 4 #2.1 Exemplar	Distilled water. Spray rinse; soak 1 h; spray rinse	Desiccation drying,1 h. Followed by SEM	Distilled water. Water bath (70 ˚C), 42 h; spray rinse	6-14% NaOCl. Shaker, 15 min	Distilled water. Spray rinse; soak 1 h; spray rinse	Desiccation drying, 1h. Followed by SEM	Distilled water. Water bath (70 ˚C), 40 h	6-14% NaOCl. Shaker, 1 h	6-14% NaOCl. Ultrasonic bath, 1 h
		Before Cleaning				After Cleaning 1			

Sample Name	10th Step	11th Step	12th Step	13th Step	14th Step	15th Step	16th Step	17th Step	18th Step
Patient 4 #1.1 Patient 4 #2.1 Exemplar	Distilled water. Spray rinse, ultrasonic bath 1h, spray rinse.	Desiccation drying,1 h. Followed by SEM	6-14% NaOCl. Shaker, 4 h	6-14% NaOCl. Ultrasonic bath, 2 h	Distilled water. Spray rinse, ultrasonic bath 1h, spray rinse.	Desiccation drying,1 h. Followed by SEM	Distilled water. Water bath (70 ˚C), 30 h	0.8 mg/ml Proteinase K. Water bath (58 ˚C), 15 h	0.8 mg/ml Proteinase K. Ultrasonic bath, 2 h
		After Cleaning 2				After Cleaning 3			

Sample Name	19th Step	20th Step	21st Step	22nd Step	23rd Step	24th Step	25th Step
Patient 4 #1.1 Patient 4 #2.1 Exemplar	Distilled water. Spray rinse, ultrasonic bath 1h, spray rinse.	Desiccation drying, 1 h. Followed by SEM	Distilled water. Water bath (70 ˚C), 48 h	6-14% NaOCl. Shaker, 17 h	6-14% NaOCl. Ultrasonic bath, 2 h.	Distilled water. Spray rinse, ultrasonic bath 1h, spray rinse.	Desiccation drying,1 h. Followed by SEM
		After Cleaning 4					After Cleaning 5

Figure 29. Patient 4 – Cleaning Protocol

Before Cleaning

The “before cleaning” samples were examined via light microscopy (LM), scanning electron microscopy (SEM), and Fourier transform infrared microscopy (FTIR-Micro). Figure 30 illustrates the appearance of a pristine TVT mesh (810041B, Lot #3694576) sample. Light microscopy analyses (Figures 31 and 32) depicts the extent to which the explanted mesh was tissue encapsulated.

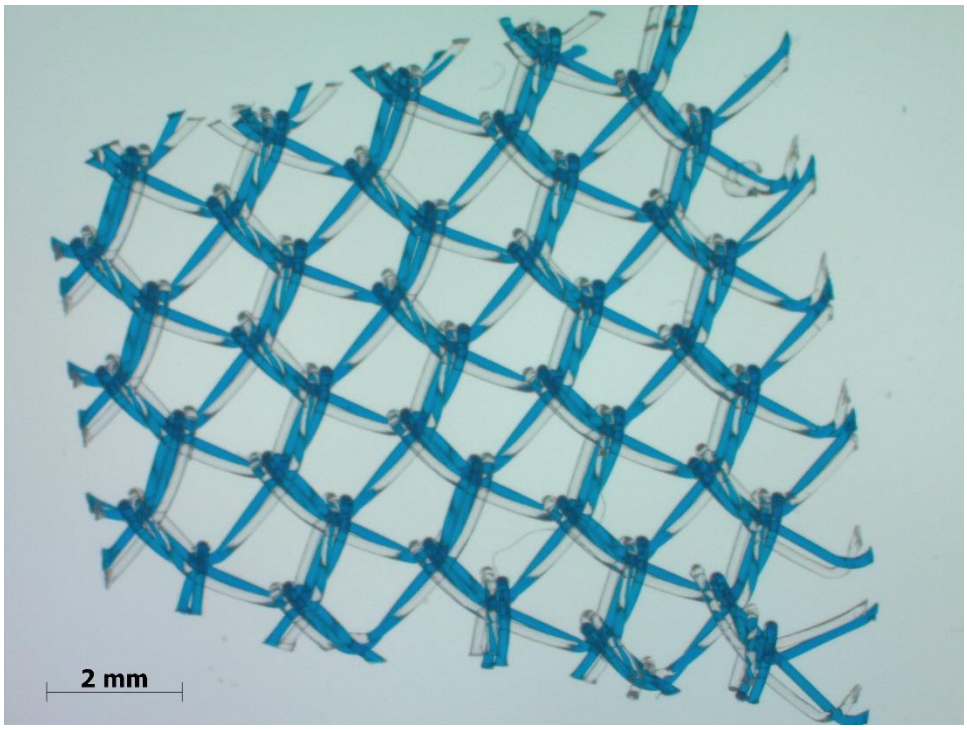


Figure 30. Pristine TVT mesh (810041B, Lot #3694576) – Before Cleaning

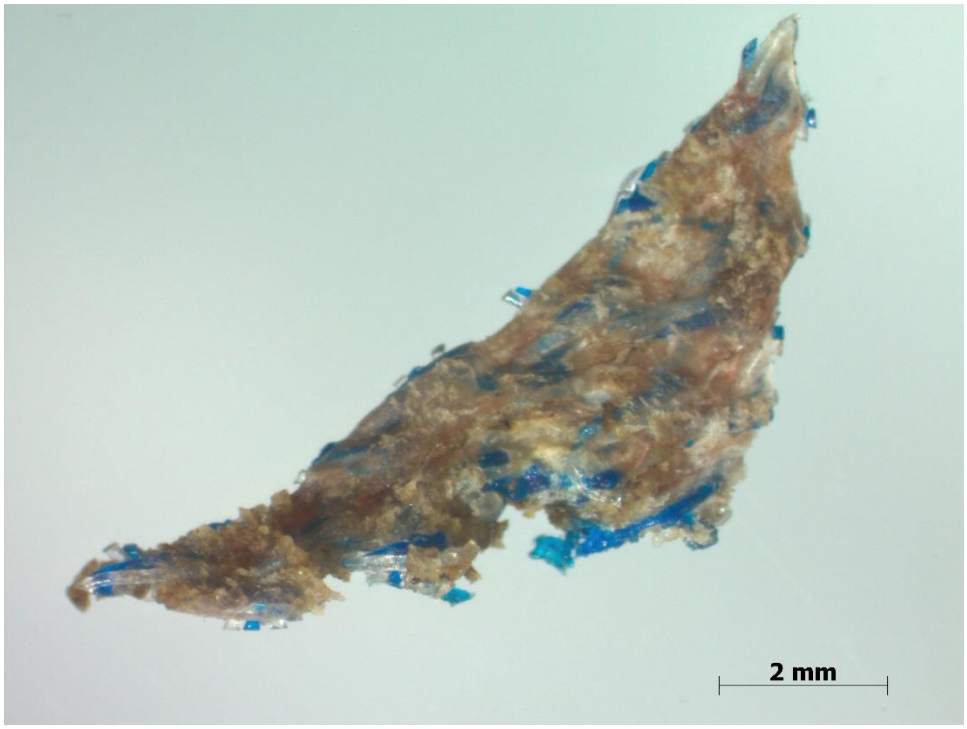


Figure 31. Patient 4 #1.1 sample – Before Cleaning

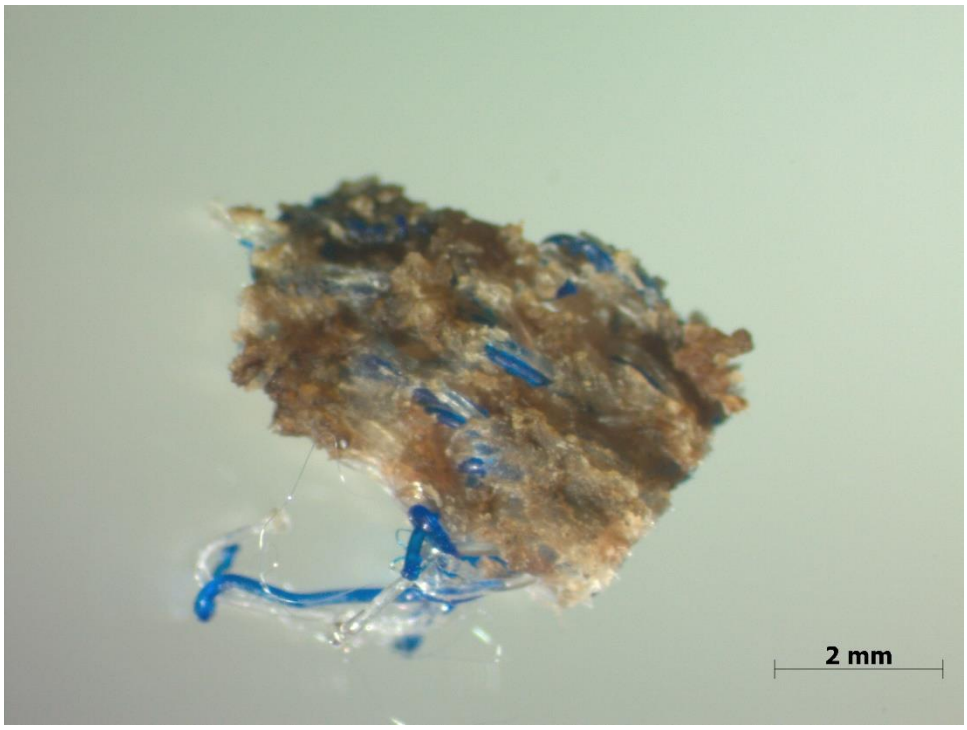


Figure 32. Patient 4 #2.1 sample – Before Cleaning

High magnification (200X) shows the Prolene fiber as it is encased within a dry and cracked, proteinaceous layer as noted in Figures 33, 34, 35, and 36, whose structure was confirmed by FTIR microscopy.

These data alone are sufficient to defeat plaintiff's consistent and incorrect tenet of *in-vivo* Prolene degradation *(*See figures 33 – 36). Plaintiffs contend, without and scientific evidence, Prolene degrades *in vivo* with concomitant cracking, loss of physical integrity and toughness, loss of molecular weight, embrittlement, and so forth. Plaintiffs allege Prolene undergoes surface cracking which leads to these property losses. However, if one simply examines Figures 33, 34, and 36, it is obvious surface cracking and peeling occurs on both the clear (unpigmented) and blue (pigmented) Prolene fibers. Plaintiffs contend the surface cracking material is degraded Prolene. However, this cannot be true. For instance, if the surface cracking and peeling material is degraded Prolene, the unpigmented and supposedly degraded Prolene fibers would be clear. Likewise, the blue and pigmented degraded Prolene fibers would be blue. However, the LM data shows unequivocally that the composition of the material peeling on <u>both</u> the clear Prolene fiber and pigmented Prolene fiber is translucent under light microscopy.

This finding does not support plaintiff's theory that the cracked material is degraded polypropylene. <u>The LM data are proof positive that the cracked and peeling product is not Prolene.</u>

To further confirm this tenet, we turned to chemical structure analysis by FTIR spectroscopy.

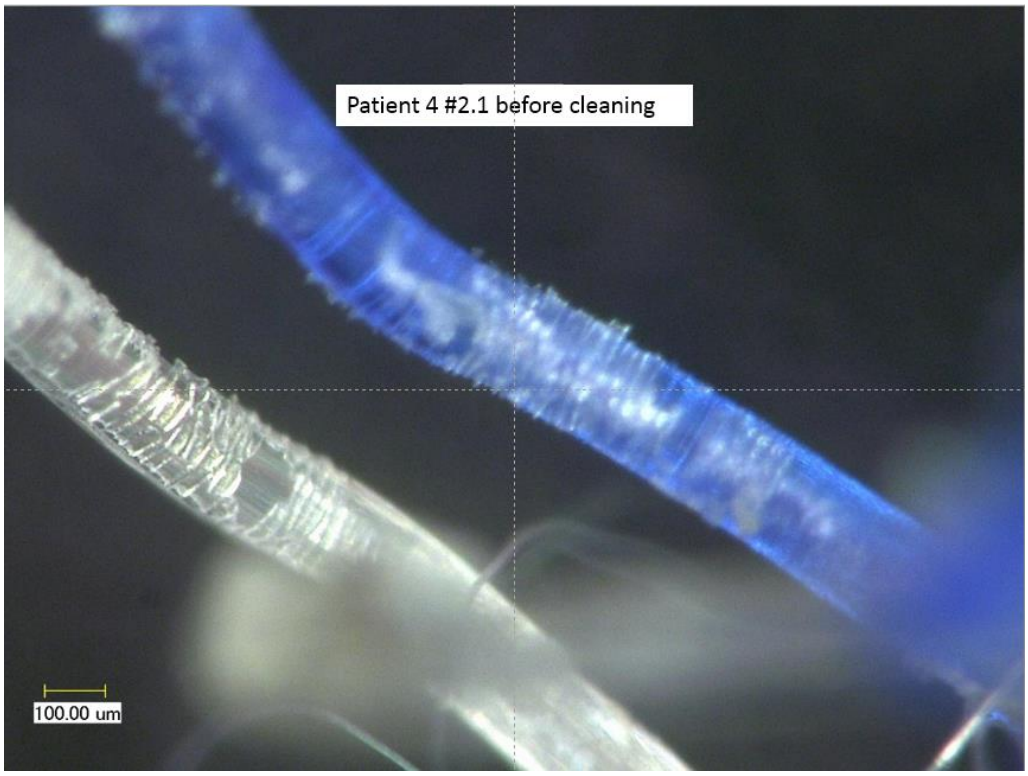


Figure 33. Patient 4 #2.1 – Before Cleaning @ 200X (Fibers outside the encapsulating tissue)

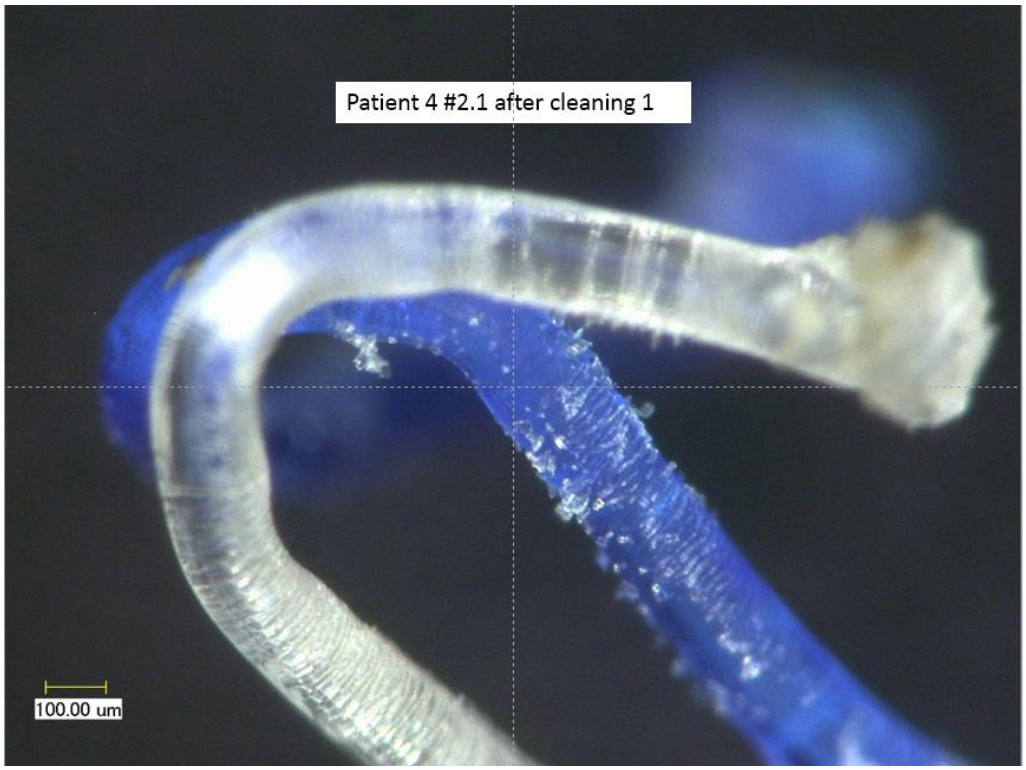


Figure 34. Patient 4 #2.1 – After Cleaning 1 @ 200X

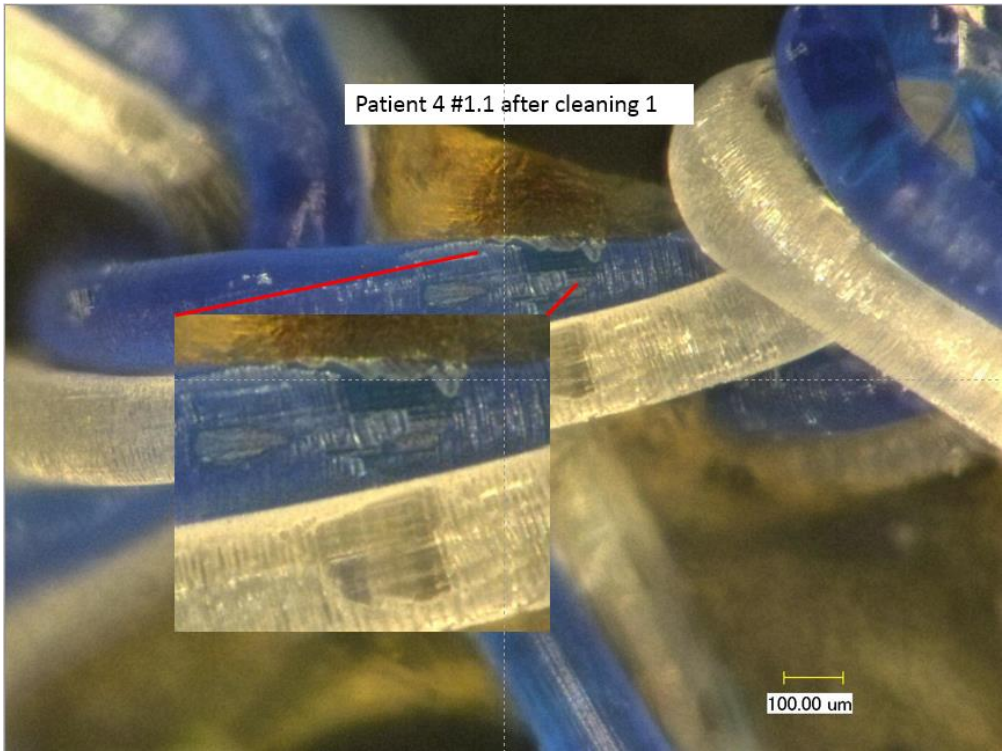


Figure 35. – Patient 4 #1.1 – After Cleaning 1 @ 200X

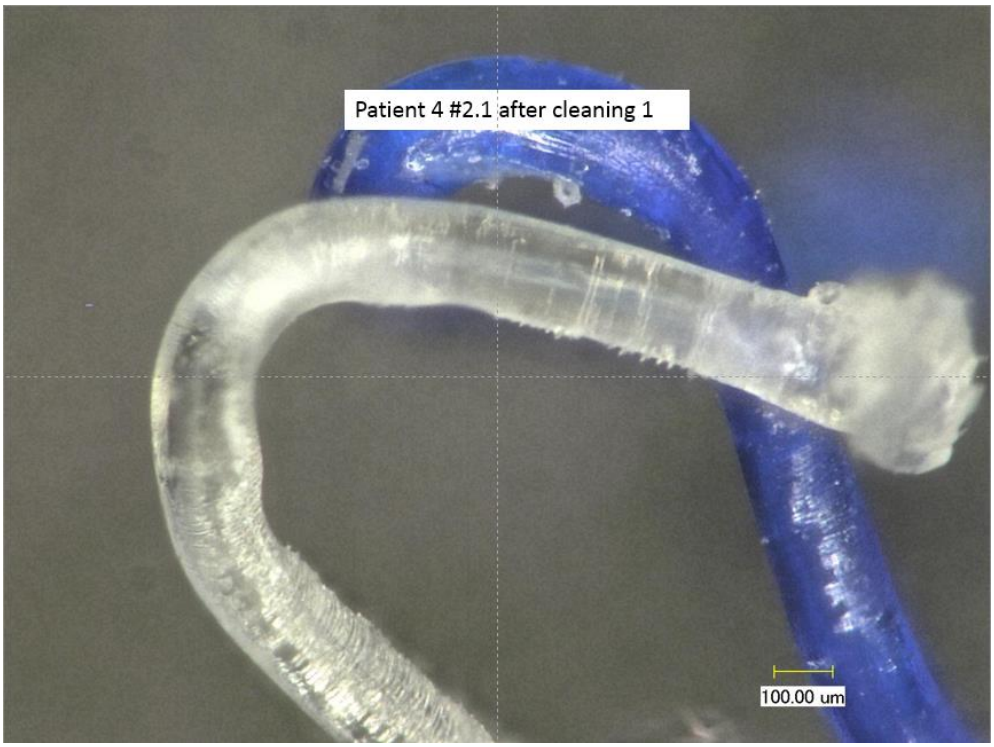


Figure 36. – Patient 4 #2.1 – After Cleaning 1 @ 200X

Chemical Structure Analysis by FTIR Spectroscopy

It is also important to note the identical translucent/clear nature of the cracked and peeled material of both the blue and clear fibers. The layer on the blue fiber is clear, not blue, again confirming its composition is not Prolene (Patient 4 #2.1). If it is degraded Prolene, it would be blue and it is not.

FTIR analyses of the flaked and peeling material from both clear and blue fibers is consistent, and further confirms the cracked and peeling materials are proteins, not Prolene.

The presence of the thin, remaining translucent protein layer on the Prolene fiber after flesh has been mechanically removed, proves strong protein adsorption and a strong adhesive bond formation between the adsorbed proteins and Prolene. The following cleaning protocol to which these samples were subjected will confirm, by scientifically collected evidence and experimentation, the extreme difficulty in removing all adsorbed proteins from Prolene.

The “Before Cleaning fiber” FTIR spectrum (Figure 37) shows spectral components of both polypropylene and proteins as noted by the highlighted 3341 and 1649 cm^{-1} frequencies. These absorption frequencies are attributed to the protein amide N-H stretching in the 3300 cm^{-1} region and amide I carbonyl stretching in the region of 1600-1690 cm^{-1} as noted by Kong *et al*., respectively.[301] Polypropylene absorption frequencies are also present at 1468 and 1381 cm^{-1} due to penetration of the IR beam through both the protein layer and into the polypropylene fiber. An overlay of the Before Cleaning fiber and Collagenase (a protein control) are included in Figure 38 demonstrating the overlap in the N-H and amide I peaks.

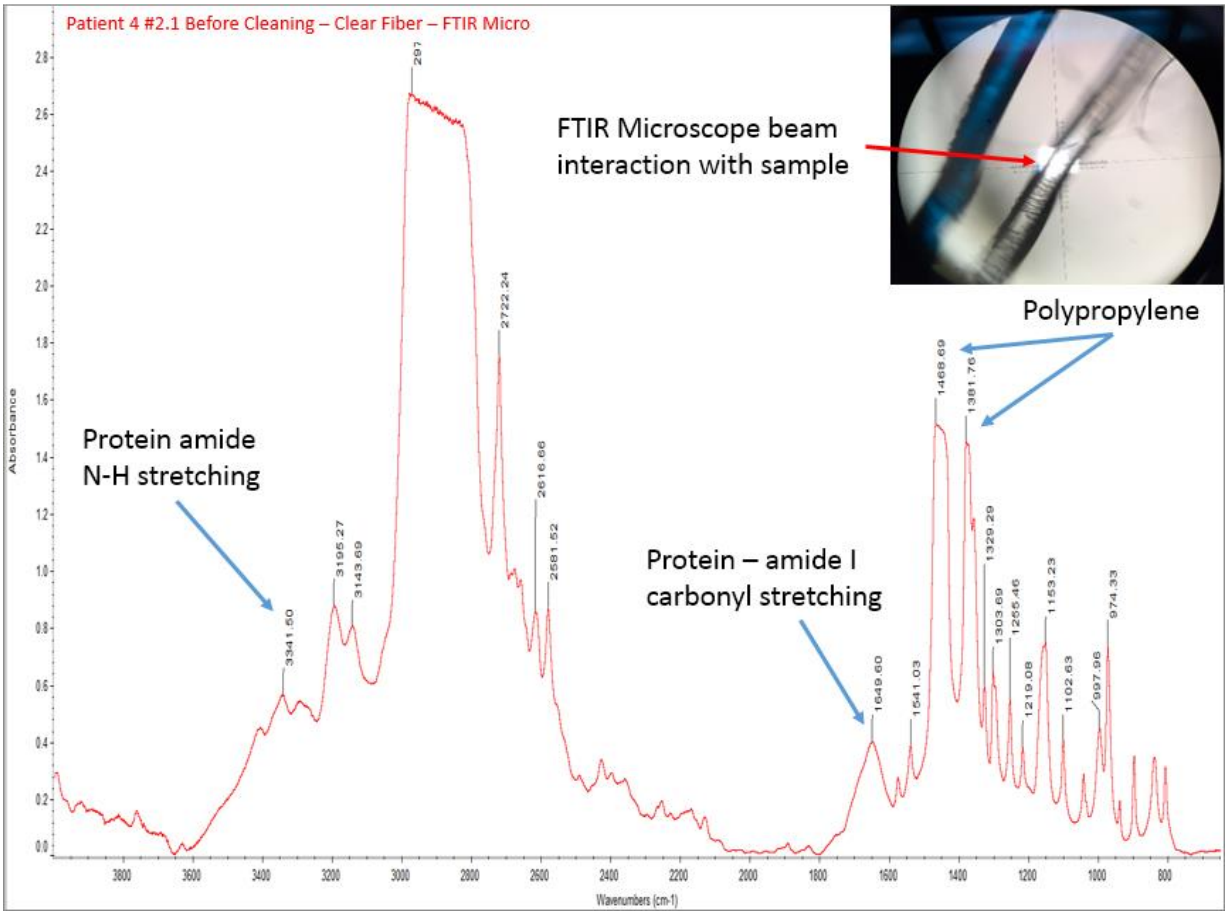


Figure 37. Patient 4 #2.1 – Clear fiber FTIR before cleaning

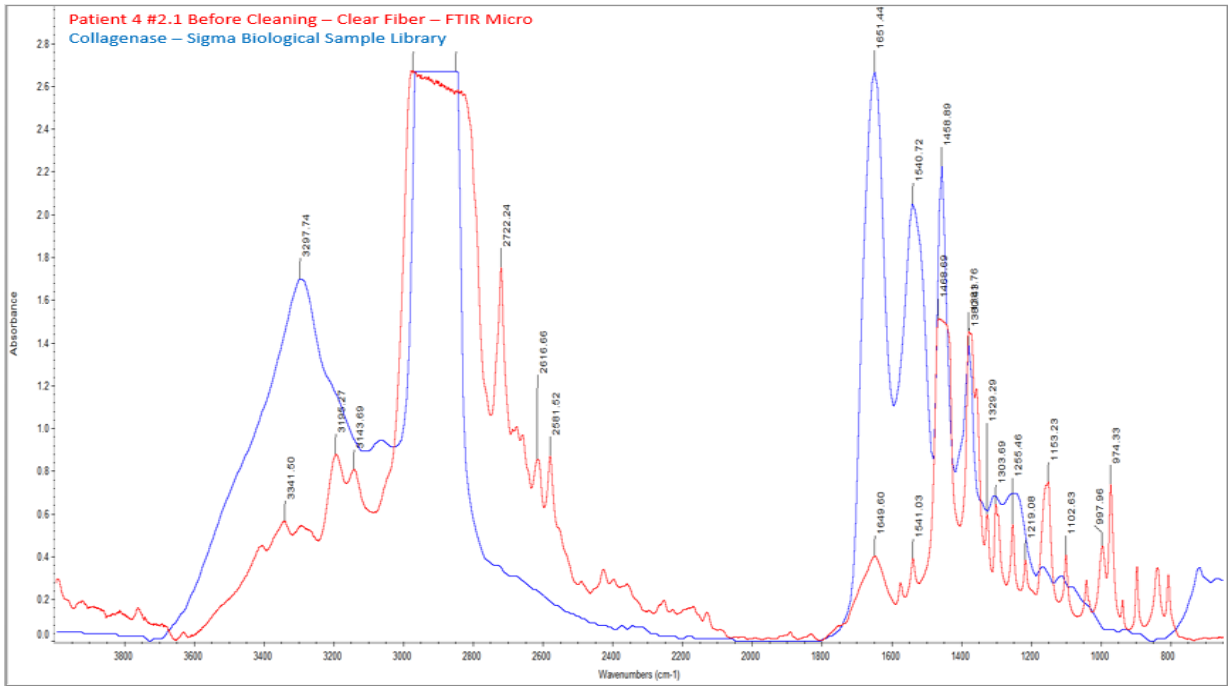


Figure 38. Patient 4 #2.1 – Clear fiber FTIR before cleaning overlaid with Collagenase

The exemplar and two explant samples were examined before cleaning and after the cleaning steps described. The data establishes a clear progression of protein removal after each cleaning step. This was confirmed both microscopically and chemically via FTIR microscopy (see the series of images in Figures 39 and 40 depicting the progressive explant cleaning).

Light Microscopy Images

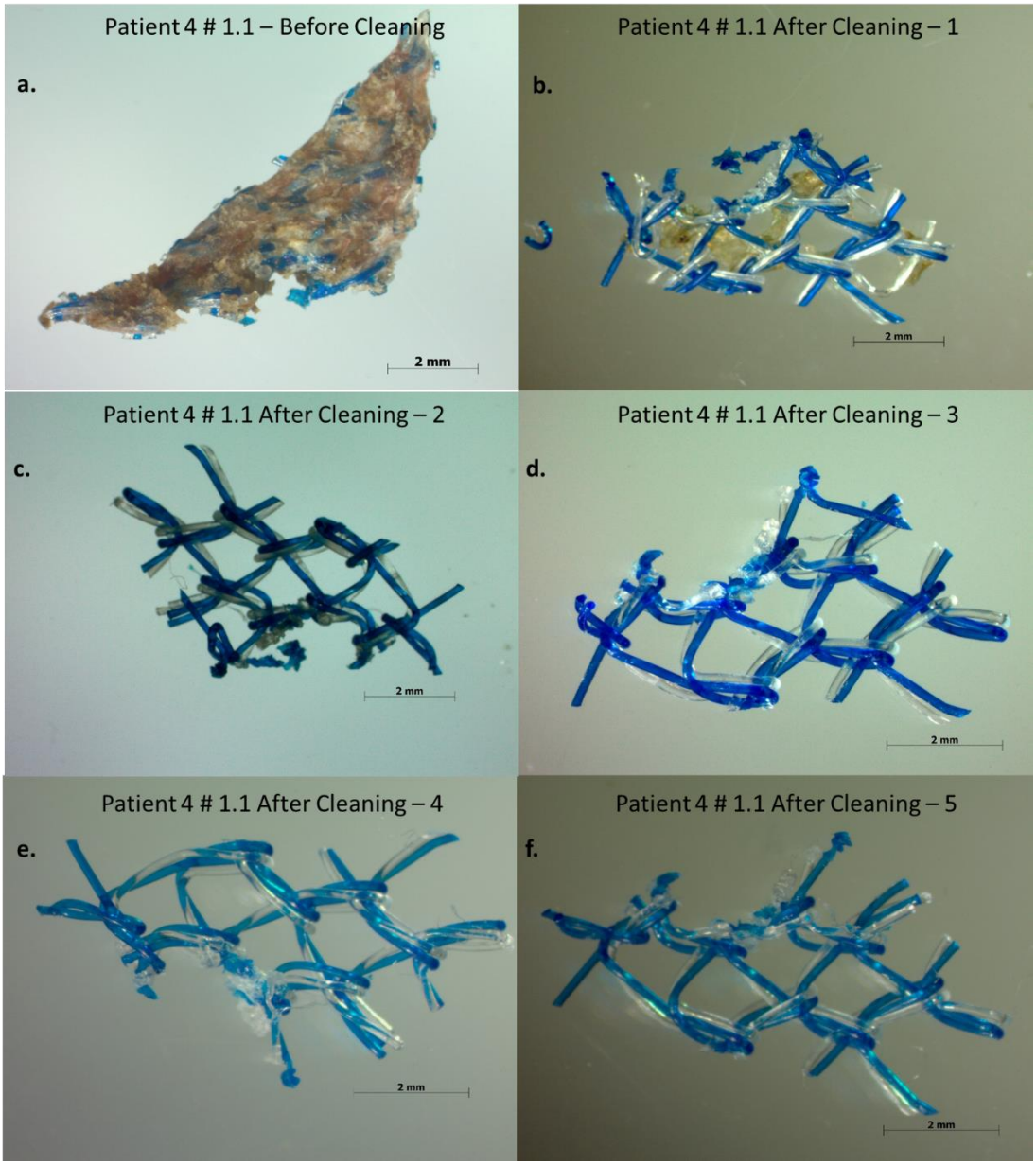


Figure 39. a., b., c., d., e., and f. – Patient 4 #1.1 Light Microscopy

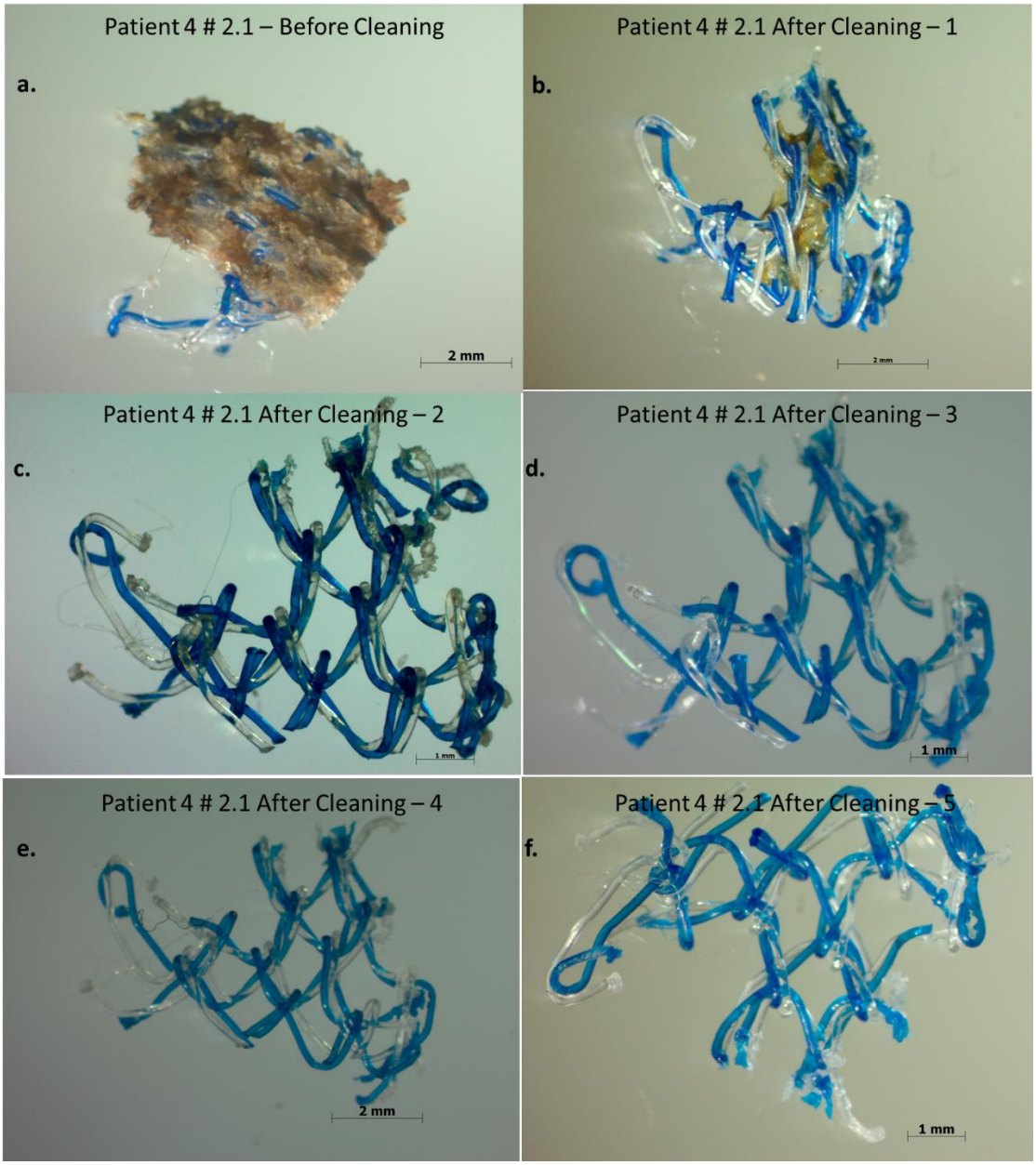


Figure 40. a., b., c., d., e., and f. – Patient 4 #2.1 Light Microscopy

Scanning Electron Microscopy (SEM) Images

SEM images at various cleaning stages depicts both the progression of explant fiber cleaning as well as the tenacity with which the Formalin-protein coating adheres to Prolene. Figures 41 b. and 42 b. define the cracked surface appearance of the fibers and its origin. The easily observable 'lock and key' pattern of the Formalin-protein coating **(Patient 4 #1.1; SEM 12)** perfectly describes cohesive failure of the Formalin-protein coating (see Figure 41 a) and adhesive failure (see Figure 41 b) of this same

Formalin-protein composite layer from Prolene (this phenomenon is present for both samples, 1.1 and 2.1).

Furthermore, the cleaning process demonstrates visually that fiber surface degradation did not occur. The SEM images of Figures 41 and 42 show partial removal of the proteinaceous shell surrounding the fiber. The cleaned fibers in Figures 41 f. and 42 f. continue to possess extrusion lines created during manufacture. If the surface of the Prolene fibers had degraded, as postulated by plaintiff's expert, the extrusion lines would likewise degrade during this process and would no longer be visible – that is not the case we observed. Therefore, surface degradation of the Patient 4 implant did not occur.

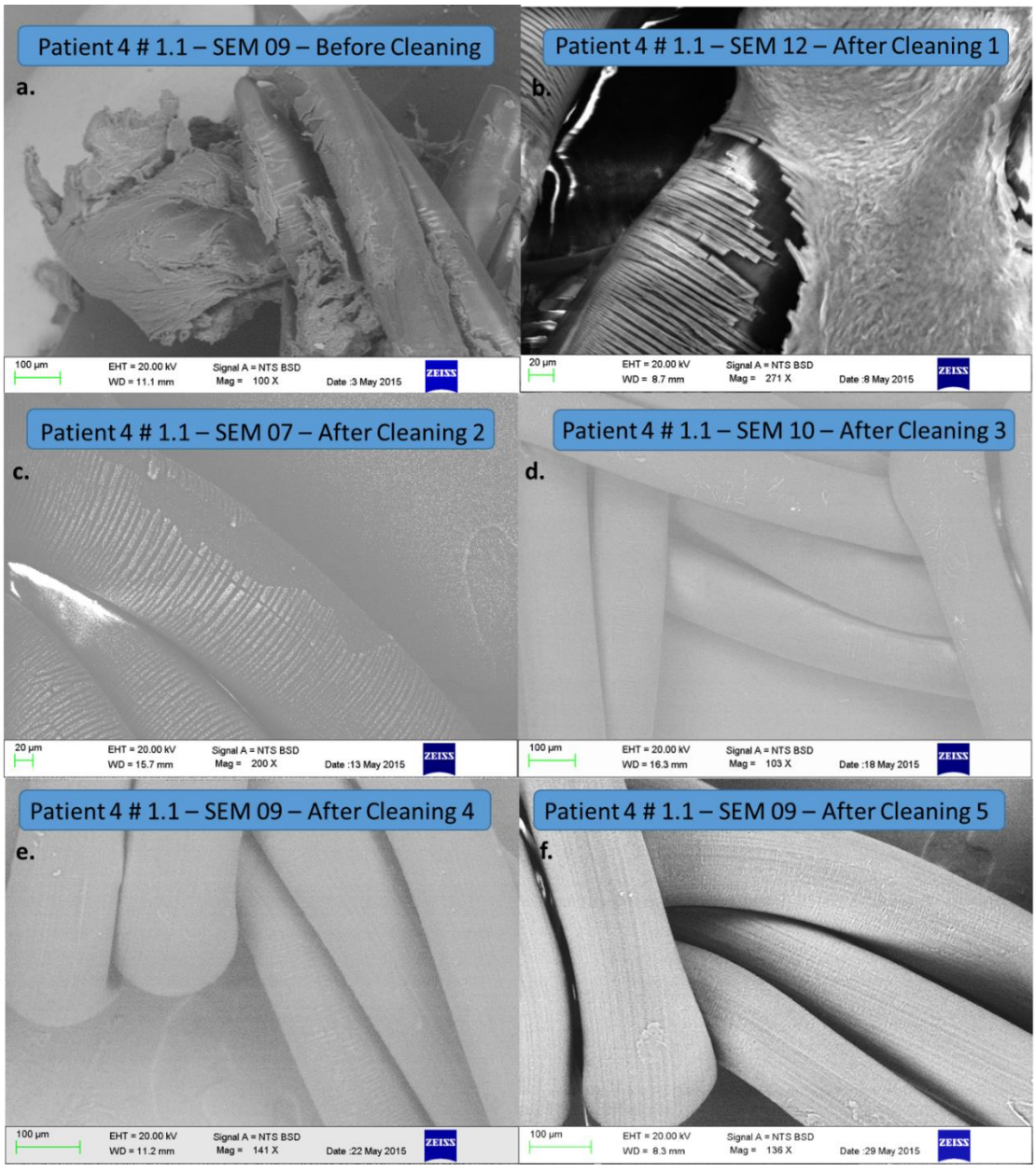


Figure 41. a., b., c., d., e., and f. – Patient 4 #1.1

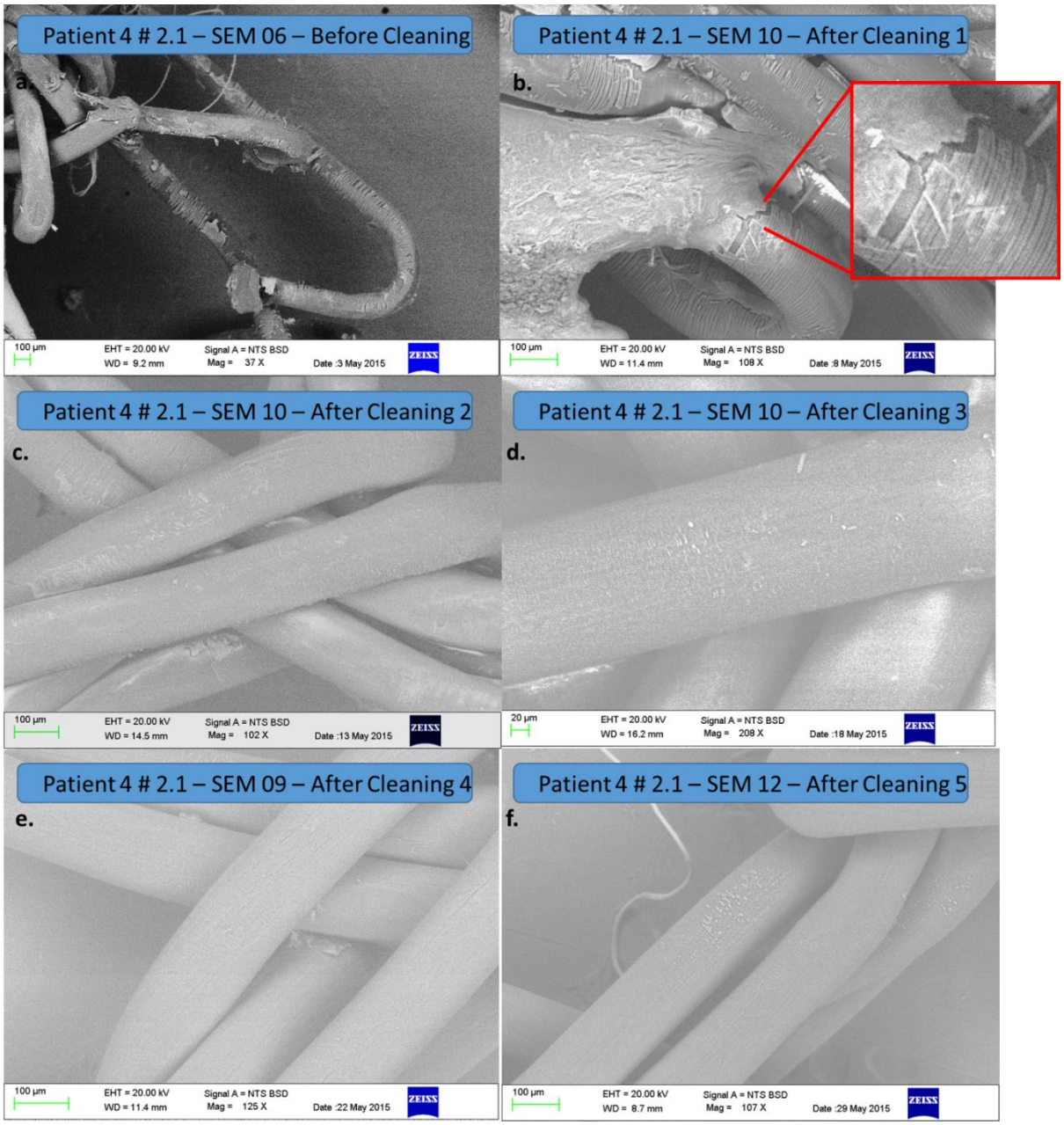


Figure 42. a., b., c., d., e., and f. – Patient 4 #2.1

FTIR analysis proves not only the presence of proteins, but continual removal of adsorbed and fixed protein as each step of the cleaning process is completed. (See

Figures 43 – 45). The spectra have been enlarged to better observe loss of protein absorption intensity with completion of each cleaning step. (Figure 45).

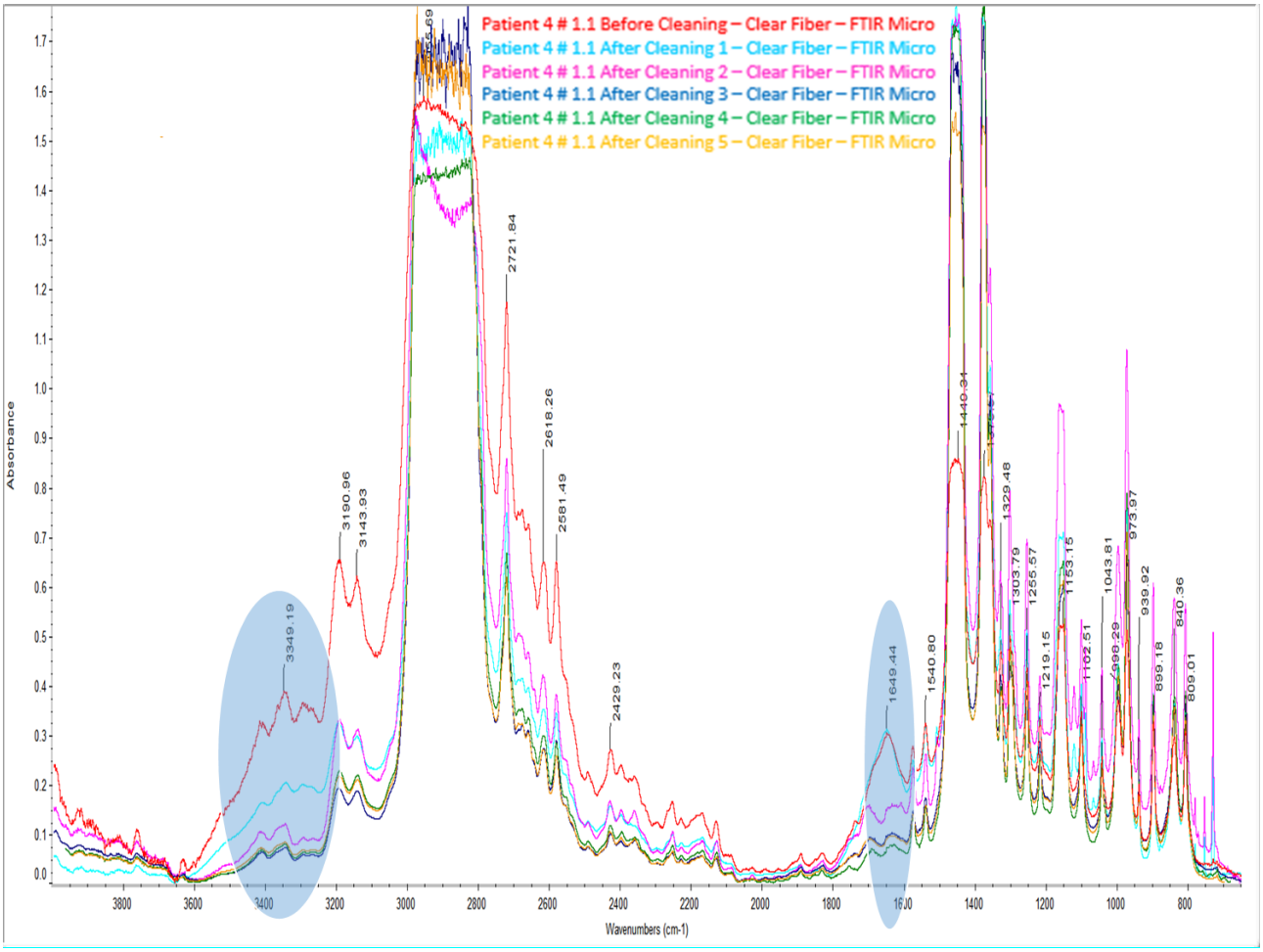


Figure 43. Patient 4 #1.1 – Progressive loss of the adsorbed protein coating with cleaning as confirmed by FTIR Spectra

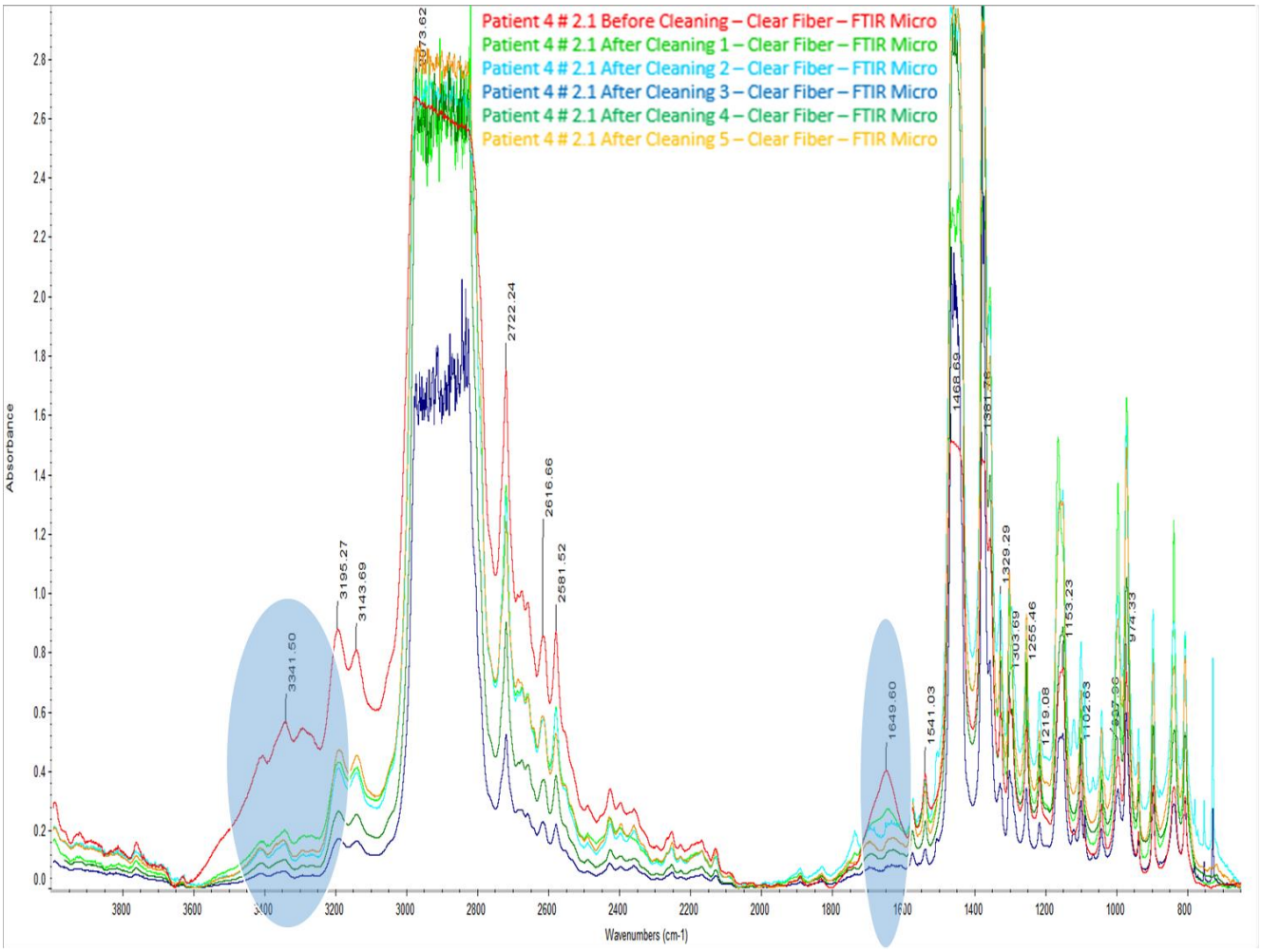


Figure 44. Patient 4 #2.1 – Progressive loss of the adsorbed protein coating with cleaning as confirmed by FTIR Spectra

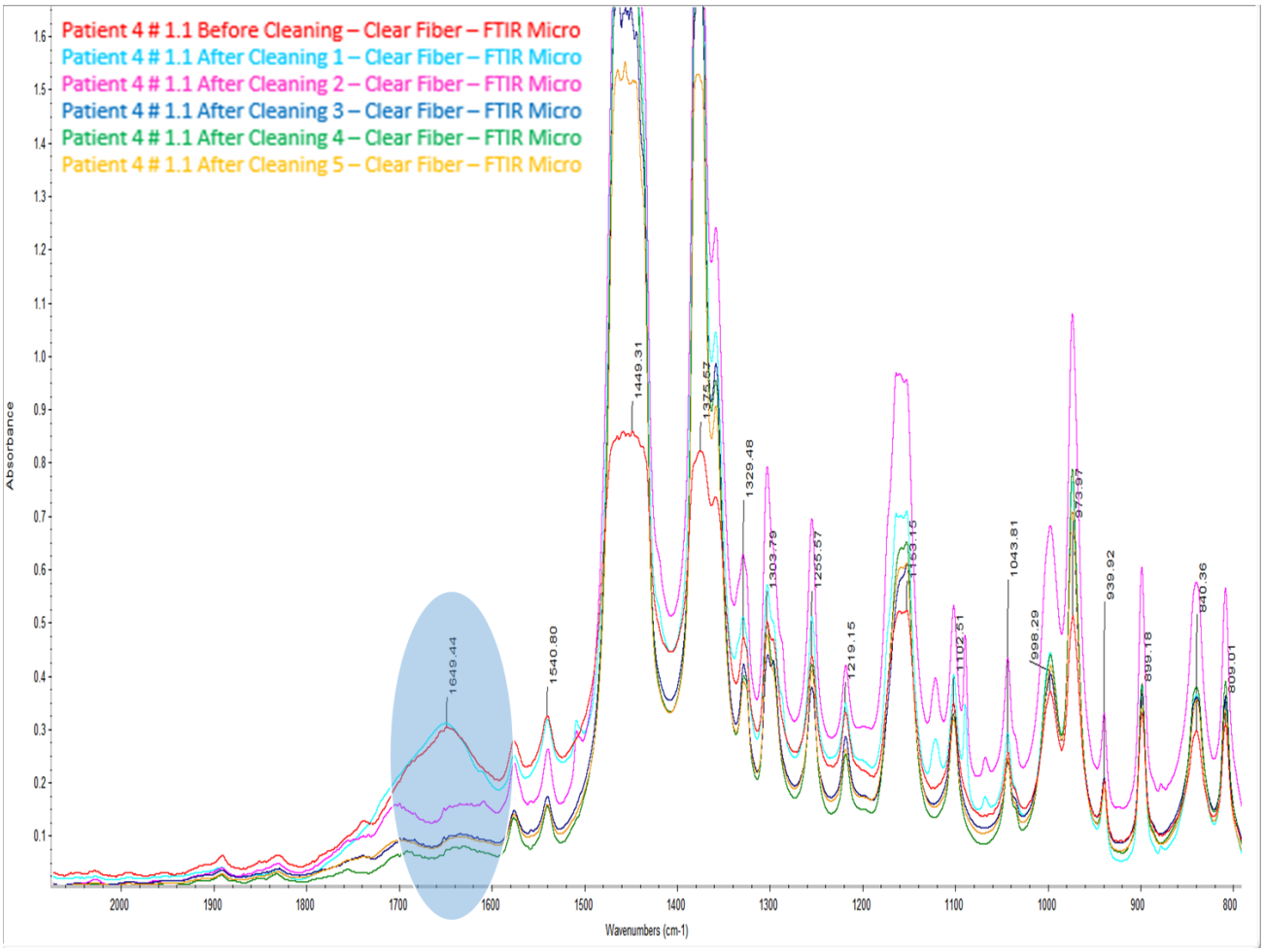


Figure 45. Patient 4 #1.1 – Progressive loss of Amide carbonyl stretching frequency with cleaning as confirmed via FTIR Microscopy – Fingerprint Region

The FTIR data proves, without question, surfaces of uncleaned explants are covered with adsorbed proteins. Collagen and other proteins chemically react with Formalin during the fixation process and form a tightly adhered, hard, brittle, insoluble composite polymeric sheath around explant fibers. Consequently, in order to remove the crosslinked protein layer one must utilize knowledge of the protein-formaldehyde chemical reaction that creates the crosslinked product. The cleaning process was developed utilizing knowledge of the protein-formaldehyde crosslinking chemistry, and therefore is an effective cleaning process. This has been affirmed by FTIR analyses of cleaned Prolene explant fibers, LM, and SEM photo-microscopy.

Flawed Methodologies by Plaintiffs' Experts

- Iakovlev has not identified or utilized a control of degraded polypropylene
- Iakovlev's opinions and statements are based on flawed methodology. They are in direct contradiction to well-established scientific principles of tissue staining

given Prolene does not possess ionic charged groups nor pH, both required for staining.

- Factors all explants have in common are, all are fixed in formaldehyde, all contain flesh, all form a formaldehyde-protein polymer or shell around PP fiber(s), and all are subjected to histologic tissue processing. This sequence of events and polymer formation, is not recognized, or is ignored, by Iakovlev.

- Iakovlev has no way to know how degraded Prolene "looks" or "takes dye" any differently than pristine Prolene since he uses no experimental control

- Iakovlev has no analytical data to confirm chemical composition of the "blue dots" and his identification of two very dissimilar materials as "blue dots." This would require analysis by FTIR microscopy or other appropriate chemical analyses.

- Guelcher's XPS data are flawed as his work shows only 4 of 17 samples possess C=O configurations while all samples contain this configuration due to the additive employed in the manufacture of Prolene.

- Guelcher's data set for potential oxidation of Prolene continues through a six week period for TVT samples, while the polypropylene control experimentation covers only four weeks.

Summary of Opinions

- Prolene used in Ethicon's Prolift and TVT products does not undergo meaningful or harmful degradation *in vivo*. My opinions are based on:

    - my personal extensive scientific investigation of the Patient 4 explant as well as other explants from similar cases,

    - the seven year dog study conducted by Ethicon in November, 1985 and reported October 15, 1992, as well as,

    - additional data and information reviewed and relied upon as referenced herein.

- Molecular weight degradation and carbonyl group formation are inextricably linked and you cannot have one without the other. Simply stated, if Prolene mesh is oxidized, its molecular weight will decrease and carbonyl bonds will form and the carbonyl bonds will show themselves in the FTIR spectra. My laboratory data has shown that explanted Prolene fibers do not exhibit carbonyl groups in the FTIR spectra and thus have not oxidized in vivo.

- Furthermore, for the explants I have examined, no evidence exists for molecular weight loss of Prolene. Thus, no Prolene degradation occurred while in vivo.

- It is my opinion, which is supported by experimental results, scientific data, and scientific literature, that proponents of *in vivo* Prolene degradation have historically, erroneously, and consistently mis-identified adsorbed and strongly adhered Proteins as Prolene and/or PP. The strongly adhered, crosslinked proteins are formed during the Formalin "fixation" process.

- Proponents of *in vivo* Prolene degradation *have* not considered well known and well established basic chemistry/polymer science principles and concepts. Consequently such proponents have promulgated mis-information and mis-interpretation and in doing so have exacerbated confusion with respect to explant analyses; specifically no consideration is given the chemical reaction of formaldehyde and proteins which forms a hard, brittle, insoluble shell around Prolene and/or PP fibers. The hard shell encases Prolene and/or PP fibers. It is this hard, brittle, insoluble, protein-formaldehyde polymer coating that has been and continues to be mis-identified as degraded Prolene.

- I am unaware of any scientifically valid data supporting the tenet of Ethicon's Prolene oxidizing or degrading *in vivo*, including the Patient 4 explant.

- The absence of meaningful, strong carbonyl absorption in Ethicon's Prolene FTIR spectra in my investigations conclusively proves the absence of Prolene degradation[179].

- The exceptional physical property data collected by Burkley, and included in his 7-year Dog Study Report, is additional proof that Prolene's physical properties did not degrade over a 7 year implantation period, but instead improved.

- I have seen no evidence suggesting rupture of Ethicon's Prolene fiber in the matter at hand, and it is my opinion that none will occur due to degradation, while used as *in vivo* implants of the type(s) investigated herein.

- There is no scientific evidence to support the contention that Ethicon's Prolene undergoes Environmental Stress Cracking *in vivo*. To the contrary, extensive evidence exists, and has been reported herein, that polypropylene does not experience Environmental Stress Cracking (ESC).

- I have not seen FTIR data confirming oxidation or any type of degradation of the Patient 4 explant or any other explants I have examined. To the contrary, my data confirms the absence of Prolene oxidation.

- At this writing I have been unable to find valid and scientifically reliable data of any type to conclusively confirm the Patient 4 explant, or any others I have examined, experienced any degradation, oxidation, hydrolysis, ESC, or loss of any physical properties as a result of *in vivo* implantation.

I reserve the right to supplement this initial report and analysis, create additional exhibits as necessary to illustrate my testimony based upon the receipt of additional

information, documents and materials, and to revise this report following the receipt of additional information and/or materials that have not yet been made available.

Shelby F. Thames, Ph.D.

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